Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Table 1. Outline of the Guidelines Development Process

Topic	Comment
Goal of the Guidelines	The guidelines provide guidance to HIV care practitioners on the optimal use of antiretroviral (ARV) agents when treating infants, children, and adolescents in early to mid-puberty (sexual maturity rating [SMR] 1–3) who are living with HIV in the United States.
Panel Members	The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) is composed of approximately 34 voting members who have expertise in the management of HIV infection in infants, children, and adolescents. Members include representatives from the Committee on Pediatric AIDS of the American Academy of Pediatrics and community representatives with knowledge of pediatric HIV infection (e.g., parents and caregivers of children and youth with HIV). The Panel also includes at least one representative from each of the following Department of Health and Human Services (HHS) agencies: the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the Health Resources and Services Administration (HRSA), and the National Institutes of Health (NIH). A representative from the Canadian Paediatric and Perinatal HIV/AIDS Research Group participates as a nonvoting, *ex officio* member of the Panel. The U.S. government representatives are appointed by their respective agencies; nongovernmental members are selected after an open announcement to call for nominations. Each member serves on the Panel for a 3-year term with an option for reappointment. A list of current members can be found in the panel roster.
Financial Disclosure	All members of the Panel submit an annual financial disclosure statement in writing, reporting any association with manufacturers of ARV drugs or diagnostics used to manage HIV infections. A list of the latest disclosures is available on the AIDS*info* website.
Users of the Guidelines	Providers of care to infants, children, and adolescents with HIV in the United States
Developer	Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV—a working group of the Office of AIDS Research Advisory Council (OARAC)
Funding Source	Office of AIDS Research, NIH, and HRSA
Evidence Collection	A standardized review of recent, relevant literature related to each section of the guidelines is performed by a technical assistance consultant (through funding from HRSA) and provided to individual Panel working groups. The recommendations are generally based on studies published in peer-reviewed journals. The Panel may occasionally use unpublished data to revise the guidelines, particularly when the new information relates to dosing or patient safety. These data come from presentations at major conferences or from the FDA and/or drug manufacturers.
Recommendation Grading	Described in Table 2
Method of Synthesizing Data	Each section of the guidelines is assigned to a small group of Panel members with expertise in the area of interest. The members synthesize the available data and propose recommendations to the Panel. The Panel discusses all proposals during monthly teleconferences. Proposals are modified based on Panel discussion and then distributed with ballots to all Panel members for concurrence and additional comments. If there are substantive comments or votes against approval, the recommended changes and areas of disagreement are brought back to the full Panel (by email or teleconference) for additional review, discussion, and further modification to reach a final version that is acceptable to all Panel members. The recommendations in these final versions represent endorsement from a consensus of members and are included in the guidelines as official Panel recommendations.
Other Guidelines	These guidelines focus on infants, children, and adolescents in early-to-mid-puberty (SMR 1–3) who are living with HIV. Guidelines for the treatment of adolescents in late puberty (SMR 4–5) are provided by the Panel on Antiretroviral Guidelines for Adults and Adolescents. Separate guidelines outline the use of antiretroviral therapy (ART) in pregnant women with HIV (including maternal and infant interventions to prevent perinatal transmission), ART for nonpregnant adults and postpubertal adolescents with HIV, and ARV prophylaxis for those who experience occupational or nonoccupational exposure to HIV. These guidelines are also available on the AIDS*info* website.
Update Plan	The full Panel meets monthly by teleconference to review data that may warrant modification of the guidelines. Smaller working groups of Panel members hold additional teleconferences to review individual drug sections or other specific topics (e.g., What to Start). Updates may be prompted by new drug approvals (or new indications, formulations, or frequency of dosing), new safety or efficacy data, or other information that may have a significant impact on the clinical care of patients. In the event of significant new data that may affect patient safety, the Panel may issue a warning announcement and post accompanying recommendations on the AIDS*info* website until the guidelines can be updated with appropriate changes. All sections of the guidelines will be reviewed at least once a year, with updates as appropriate.

Table 2. Rating Scheme for Recommendations

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement **B:** Moderate recommendation for the statement **C:** Optional recommendation for the statement	**I:** One or more randomized trials **in children**[a] with clinical outcomes and/or validated laboratory endpoints **I*:** One or more randomized trials **in adults**, with clinical outcomes and/or validated laboratory endpoints plus accompanying data **in children**[a] from one or more well-designed, nonrandomized trials or observational cohort studies with clinical outcomes **II:** One or more well-designed, nonrandomized trials or observational cohort studies **in children**[a] with clinical outcomes **II*:** One or more well-designed, nonrandomized trials or observational cohort studies **in adults** with clinical outcomes plus accompanying data **in children**[a] from one or more smaller nonrandomized trials or cohort studies with clinical outcome data **III:** Expert opinion

[a] These are studies that include children or children and adolescents, but not studies that are limited to postpubertal adolescents.

Table 3. Sample Schedule for Clinical and Laboratory Monitoring of Children Before and After Initiation of Antiretroviral Therapy

Laboratory Testing	Entry Into Care[a]	Pre-Therapy[b]	ART Initiation[c]	Weeks 1–2 on Therapy	Weeks 2–4 on Therapy	Every 3–4 Months[d]	Every 6–12 Months[e]	Virologic Failure (Prior to Switching ARV Regimens)
Medical History and Physical Examination[f]	√	√	√	√	√	√		√
Adherence Evaluation		√	√	√	√	√		√
CD4 Count	√	√	√			√		√
Plasma Viral Load	√	√	√		√	√		√
Resistance Testing	√							√
CBC with Differential	√	√	√		√	√		√
Chemistries[g]	√	√	√		√	√		√
Lipid Panel	√		√				√	
Random Plasma Glucose[h]			√				√	
Urinalysis	√		√				√	
HBV Screening[i]		√						√
Pregnancy Test for Women of Childbearing Age[j]		√						√

[a] See text for details on recommended laboratory tests to perform.

[b] A patient's ability to adhere to an ARV regimen is assessed prior to starting ART. When ABC is being considered as part of the regimen, send HLA-B*5701 testing prior to initiating ABC and choose an alternative ARV drug if the patient is HLA-B*5701 positive (see the Abacavir section in Appendix A: Pediatric Antiretroviral Drug Information). Genotype resistance testing is recommended if it has not already been performed (see Drug-Resistance Testing in the Adult and Adolescent Antiretroviral Guidelines). Send tests that are appropriate for the toxicity profile that is associated with the patient's ARV regimen and the patient's medical history (see text).

[c] If ART is initiated within 30 days to 90 days of a pre-therapy lab result, repeat testing may not be necessary.

[d] CD4 cell count, CBC, and chemistries can be monitored less frequently (every 6–12 months) in children and youth who are adherent to therapy, who have CD4 cell count values that are well above the threshold for OI risk, and who have had sustained virologic suppression and stable clinical status for more than 2–3 years. Viral load testing every 3–4 months is generally recommended to monitor ARV adherence.

[e] If lipid levels have been abnormal in the past, more frequent monitoring may be needed. For patients treated with TDF, more frequent urinalysis should be considered.

[f] Pay special attention to changes in weight that might occur after altering an ARV regimen. Weight gain or weight loss may occur when using some ARV drugs (see Table 15h– Lipodystrophies and Weight Gain).

[g] Chemistries refer to a comprehensive metabolic panel.

[h] Random plasma glucose is collected in a gray-top blood collection tube or other designated tube.

[i] This screening is only recommended for individuals who have previously demonstrated no immunity to HBV and who are initiating a regimen that contains ARV drugs with activity against HBV, specifically 3TC, FTC, TAF, or TDF.

[j] See the Adult and Adolescent Antiretroviral Guidelines, as well as Preconception Counseling and Care for Women of Childbearing Age Living with HIV in the Perinatal Guidelines.

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; CBC = complete blood count; CD4 = CD4 T lymphocyte; FTC = emtricitabine; HBV = hepatitis B virus; OI = opportunistic infection; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Table 4. Primary Food and Drug Administration-Approved Assays for Monitoring Viral Load

Assay	Abbott Real Time	NucliSens EasyQ v2.0	COBAS AmpliPrep/ TaqMan v2.0	Versant v1.0	Aptima HIV-1 Quant Assay
Method	Real-time RT-PCR	Real-time NASBA	Real-time RT-PCR	Real-time RT-PCR	Real-time TMA
Dynamic Range	40–10^7 copies/mL	25–10^7 copies/mL	20–10^7 copies/mL	37–11x10^7 copies/mL	30–10^7 copies/mL
Specimen Volume[a]	0.2–1 mL	0.1–1 mL	1 mL	0.5 mL	≥0.4 mL
Manufacturer	Abbott Laboratories	bioMerieux	Roche	Siemens	Hologic, Inc.

[a] Smaller volumes for children can be accommodated.

Key: NASBA = nucleic acid sequence-based amplification; RT-PCR = reverse transcription polymerase chain reaction; TMA = transcription-mediated amplification

Table 5. HIV Infection Stage Based on Age-Specific CD4 Count or Percentage

Stage[a]	Aged <1 Year		Aged 1 Year to <6 Years		Aged ≥6 Years	
	Cells/mm^3	%	Cells/mm^3	%	Cells/mm^3	%
1	≥1,500	≥34	≥1,000	≥30	≥500	≥26
2	750–1,499	26–33	500–999	22–29	200–499	14–25
3	<750	<26	<500	<22	<200	<14

[a] The stage is based primarily on the CD4 count; the CD4 count takes precedence over the CD4 percentage, and the percentage is considered only when the count is missing. If a Stage 3-defining condition has been diagnosed (see Table 6), then the stage is 3 regardless of CD4 test results.

Source: Centers for Disease Control and Prevention. Revised surveillance case definition for HIV infection—United States, 2014. *MMWR* 2014;63(No. RR-3):1-10.

Key: CD4 = CD4 T lymphocyte

Table 6. HIV-Related Symptoms and Conditions (page 1 of 2)

Mildly Symptomatic
Children with two or more of the following conditions, but none of the conditions listed in the Moderately Symptomatic category, are considered mildly symptomatic:
• Lymphadenopathy (lymph nodes are ≥0.5 cm at more than two sites and/or bilateral at one site)
• Hepatomegaly
• Splenomegaly
• Dermatitis
• Parotitis
• Recurrent or persistent upper respiratory tract infection, sinusitis, or otitis media
Moderately Symptomatic
• Anemia (hemoglobin <8 g/dL [<80 g/L]), neutropenia (white blood cell count <1,000 per µL [$<1.0 \times 10^9$ per L]), and/or thrombocytopenia (platelet count $<100 \times 10^3$ per µL [$<100 \times 10^9$ per L]) persisting for ≥30 days
• Bacterial meningitis, pneumonia, or sepsis (single episode)
• Candidiasis, oropharyngeal (thrush), persisting for >2 months in children aged >6 months
• Cardiomyopathy
• CMV infection, with onset before age 1 month
• Diarrhea, recurrent or chronic
• Hepatitis
• HSV stomatitis, recurrent (more than two episodes within 1 year)
• HSV bronchitis, pneumonitis, or esophagitis with onset before age 1 month
• Herpes zoster (shingles) involving at least two distinct episodes or more than one dermatome
• Leiomyosarcoma
• Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex
• Nephropathy
• Nocardiosis
• Persistent fever (lasting >1 month)
• Toxoplasmosis, onset before age 1 month
• Varicella, disseminated (complicated chickenpox)
AIDS-Defining Conditions
• Bacterial infections, multiple or recurrent[a]
• Candidiasis of bronchi, trachea, or lungs
• Candidiasis of esophagus
• Cervical cancer, invasive
• Coccidioidomycosis, disseminated or extrapulmonary
• Cryptococcosis, extrapulmonary
• Cryptosporidiosis, chronic intestinal (>1 month duration)
• CMV disease (other than liver, spleen, or lymph nodes), onset at age >1 month
• CMV retinitis (with loss of vision)
• Encephalopathy attributed to HIV[b]
• HSV: chronic ulcers (>1 month duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)
• Histoplasmosis, disseminated or extrapulmonary
• Isosporiasis, chronic intestinal (>1 month duration)
• Kaposi sarcoma
• Lymphoma, Burkitt (or equivalent term)
• Lymphoma, immunoblastic (or equivalent term)
• Lymphoma, primary, of brain
• *Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated or extrapulmonary

Table 6. HIV-Related Symptoms and Conditions (page 2 of 2)

AIDS-Defining Conditions, continued
• *Mycobacterium* tuberculosis of any site, pulmonary, disseminated, or extrapulmonary
• *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
• *Pneumocystis jirovecii* (previously known as *Pneumocystis carinii*) pneumonia
• Pneumonia, recurrent[c]
• Progressive multifocal leukoencephalopathy
• Salmonella septicemia, recurrent
• Toxoplasmosis of brain, onset at age >1 month
• Wasting syndrome attributed to HIV[b]

[a] Only among children aged <6 years.

[b] Suggested diagnostic criteria for these illnesses, which might be particularly important for HIV encephalopathy and HIV wasting syndrome, are described in the following references:

Centers for Disease Control and Prevention. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR*. 1994;43(No. RR-12).

Centers for Disease Control and Prevention. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR*. 1992;41(No. RR-17).

[c] Only among adults, adolescents, and children aged ≥6 years.

Key: CMV = cytomegalovirus; HSV = herpes simplex virus

Modified from:

Centers for Disease Control and Prevention. 1994 revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR*. 1994;43(No. RR-12).

Centers for Disease Control and Prevention: Revised Surveillance Case Definition for HIV Infection—United States, 2014. *MMWR*. 2014;63(No. RR-3):1-10.

Table 7. Antiretroviral Regimens Recommended for Initial Therapy for HIV Infection in Children

An ARV regimen for treatment-naive children is generally made up of a two-NRTI backbone and either one NNRTI **or** one INSTI **or** one PI boosted with RTV or COBI. Regimens are designated *Preferred* based on efficacy, ease of administration, and acceptable toxicity. *Alternative* regimens have also demonstrated efficacy, but clinical experience with these regimens is limited or these regimens are more difficult to administer than *Preferred* regimens. Regimens should be tailored to the individual patient by weighing the advantages and disadvantages of each combination. Many agents have multiple formulations and age and weight recommendations. Please consult Appendix A: Pediatric Antiretroviral Drug Information for additional information and recommended doses and formulations (see Table 8 below).

Children who are receiving effective and tolerable ARV regimens can continue using those regimens as they age, even if the combinations they are receiving are no longer *Preferred* regimens.

Preferred Regimens			
Age	**Regimens**		**FDC Available** (see Appendix A, Table 1)
Infants, Birth to Age <14 Days[a,b]	Two NRTIs **plus** NVP		No
	Weight ≥2 kg	Two NRTIs **plus** RAL[c]	No
Children Aged ≥14 Days to <3 Years	Two NRTIs **plus** LPV/r[b]		No
	Weight ≥2 kg	Two NRTIs **plus** RAL[c]	No
Children Aged ≥3 Years	Weight <25 kg	Two NRTIs **plus** ATV/r	No
		Two NRTIs **plus** twice-daily DRV/r[d]	No
		Two NRTIs **plus** RAL[c]	No
	Weight ≥25 kg	Two NRTIs **plus** DTG[e]	Yes
		Two NRTIs **plus** EVG/c[f]	Yes
Adolescents Aged ≥12 Years with SMRs of 1–3	Weight ≥25 kg	Two NRTIs **plus** BIC[g]	Yes
Adolescents Aged ≥12 Years with SMRs of 4 or 5	Refer to the Adult and Adolescent Antiretroviral Guidelines		Yes
Alternative Regimens			
Age	**Regimens**		**FDC Available** (see Appendix A, Table 1)
Children Aged ≥14 Days to <3 Years	Two NRTIs **plus** NVP[h]		No
Children Aged ≥3 Months to <3 Years	Two NRTIs **plus** ATV/r		No
Children Aged ≥3 Years	Weight ≥20 kg to <25 kg	Two NRTIs **plus** DTG[e]	No
Children Aged ≥3 Years	Weight ≥25 kg	Two NRTIs **plus** ATV/r	No
		Two NRTIs **plus** DRV/r[d]	No
		Two NRTIs **plus** RAL[c]	No
Children Aged ≥3 Years	Two NRTIs **plus** EFV[i]		No[j]
	Two NRTIs **plus** LPV/r		No
Children Aged ≥6 Years to <12 Years	Weight ≥25 kg	Two NRTIs **plus** BIC[g]	Yes
Adolescents Aged ≥12 Years with SMRs of 1–3	Weight ≥35 kg	Two NRTIs **plus** RPV[k]	Yes
		Two NRTIs **plus** ATV/c	No[j]
	Weight ≥40 kg	Two NRTIs **plus** DRV/c[l]	Yes
Adolescents Aged ≥12 Years with SMRs of 4 or 5	Refer to the Adult and Adolescent Antiretroviral Guidelines		Yes
Preferred Dual-NRTI Backbone Options for Use in Combination with Other Drugs			
Age	**Dual-NRTI Backbone Options**		**FDC Available**
Children, Birth to Age <3 Months	ZDV **plus** (3TC **or** FTC)[m]		No[j]

Table 7. Antiretroviral Regimens Recommended for Initial Therapy for HIV Infection in Children, continued

Preferred Dual-NRTI Backbone Options for Use in Combination with Other Drugs, continued			
Age	**Dual-NRTI Backbone Options**		**FDC Available**
Children Aged ≥3 Months to <6 Years	ABC **plus** (3TC[n] **or** FTC)		Yes
	ZDV **plus** (3TC[m] **or** FTC)		Yes
Children and Adolescents Aged ≥6 Years with SMRs of 1–3	ABC **plus** (3TC[n] **or** FTC)		Yes
	Weighing ≥25 kg and receiving a regimen that contains an INSTI or an NNRTI	FTC/TAF[o]	Yes
Adolescents Aged ≥12 Years with SMRs of 4 or 5	Refer to the Adult and Adolescent Antiretroviral Guidelines		Yes
Alternative Dual-NRTI Backbone Options for Use in Combination with Other Drugs			
Age	**Dual-NRTI Backbone Options**		**FDC Available**
Children Aged ≥3 Months	ZDV **plus** ABC		No
Children Aged ≥2 Years to 12 Years	TDF **plus** (3TC **or** FTC)[p]		Yes
Children and Adolescents Aged ≥6 Years and SMRs of 1–3	ZDV **plus** (3TC **or** FTC)[m]		Yes

[a] If treatment is scheduled to begin before a patient is aged 14 days, NVP or RAL are *Preferred* agents because they are the only options with dosing information available for this age group. While many pediatric experts favor initiating ART as soon as possible after birth in order to limit the establishment of viral reservoirs, available clinical trial data does not suggest that initiating treatment within the first 14 days of life leads to better clinical outcomes than initiating treatment after 14 days of age. Clinicians should consult an expert in pediatric HIV infection before initiating treatment in infants aged <14 days. Additional considerations regarding the use of NVP or RAL in infants aged <14 days can be found in Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection. Switching from NVP to LPV/r should be considered when the infant is aged ≥14 days with a postmenstrual age of 42 weeks (the span of time between the first day of the mother's last menstrual period and birth, plus the time elapsed after birth); LPV/r has produced better clinical outcomes in studies of children aged <3 years than NVP. Data are limited on the clinical outcomes of using RAL in infants and children aged <2 years.

[b] In general, LPV/r **should not be administered** to neonates before a postmenstrual age of 42 weeks and postnatal age ≥14 days (see the Lopinavir/Ritonavir section in Appendix A: Pediatric Antiretroviral Drug Information).

[c] RAL pills or chewable tablets can be used in children aged ≥2 years. Granules can be administered in infants and children from birth to age 2 years. No dosing information is available for preterm infants or those weighing <2 kg at birth.

[d] DRV should only be used in children weighing ≥10 kg. Once-daily DRV should not be used in children aged <12 years or weighing <40 kg. Once-daily DRV should also not be used when any one of the following resistance-associated substitutions are present: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V. DRV/r is recommended as an *Alternative* drug combination for children aged ≥6 years to <12 years and weighing >25 kg, because there are other drugs that can be administered once daily and that are better tolerated. Note that DRV/r can be administered once daily in adolescents aged ≥12 years and weighing ≥40 kg who are not sexually mature (SMR 1–3).

[e] DTG is recommended as a *Preferred* agent for children and adolescents aged ≥3 years and weighing ≥25 kg. It is recommended as an *Alternative* agent in children aged ≥3 years and weighing 20 kg to <25 kg. An FDC tablet that contains ABC/DTG/3TC (Triumeq) is available for children weighing ≥25 kg.

[f] EVG is currently recommended only as a component of FDC tablets. Tablets that contain EVG/c/FTC/TAF (Genvoya) are recommended as a *Preferred* regimen for children and adolescents weighing ≥25 kg.

[g] BIC is available only as part of an FDC tablet that contains BIC/FTC/TAF (Biktarvy); this FDC tablet is recommended as a *Preferred* regimen for adolescents aged ≥12 years and weighing ≥25 kg. It is recommended as an Alternative regimen for children aged ≥6 years and weighing ≥25 kg.

[h] NVP should not be used in post-pubertal girls with CD4 counts >250/mm^3, unless the benefit clearly outweighs the risk. NVP is approved by the FDA for treatment of infants aged ≥15 days.

[i] EFV is approved by the FDA for use in children aged ≥3 months and weighing ≥3.5 kg, but **it is not recommended** by the Panel for initial therapy in children aged ≥3 months to 3 years. FDC tablets that contain EFV/FTC/TDF (Atripla) and EFV 600 mg/3TC/TDF (Symfi) are available. See the Efavirenz section in Appendix A: Pediatric Antiretroviral Drug Information for information about use of the FDC EFV 400 mg/3TC/TDF (Symfi Lo).

[j] FDA-approved FDC tablets are not included in this table when they are not approved for use in the specific patient populations being discussed.

[k] RPV should be administered to adolescents aged ≥12 years and weighing ≥35 kg who have initial viral loads ≤100,000 copies/mL. FDC tablets that contain FTC/RPV/TAF (Odefsey) and FTC/RPV/TDF (Complera) are available.

Table 7. Antiretroviral Regimens Recommended for Initial Therapy for HIV Infection in Children, continued

[l] DRV/c is available as part of an FDC tablet containing DRV/c/FTC/TAF (Symtuza) that has been approved by the FDA for use in children and adolescents weighing ≥40 kg.

[m] An FDC tablet that contains 3TC/ZDV (Combivir and generic) is available for use in children weighing ≥30 kg.

[n] An FDC tablet that contains ABC/3TC (Epzicom and generic) is available for use in children weighing ≥25 kg.

[o] FTC plus TAF is recommended as a *Preferred* combination for children and adolescents weighing ≥25 kg; an FDC tablet that contains FTC/TAF (Descovy) is available. FTC/TAF is approved by the FDA for children weighing ≥25 kg when used in the single-tablet regimen EVG/c/FTC/TAF or as TAF/FTC in combination with an NNRTI or INSTI. FTC/TAF plus a boosted PI is only recommended for use in children and adolescents weighing ≥35 kg.

[p] An FDC tablet that contains FTC/TDF (Truvada) is available.

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; CD4 = CD4 T lymphocyte; COBI = cobicistat; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDA = Food and Drug Administration; FDC = fixed-dose combination; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; the Panel = the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SMR = sexual maturity rating; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children (page 1 of 4)

See Appendix A: Pediatric Antiretroviral Drug Information and Table 7. Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios in the Adult and Adolescent Antiretroviral Guidelines for more information.

ARV Class	ARV Agent(s)	Advantages	Disadvantages
INSTIs In Alphabetical Order	All INSTIs	**INSTI Class Advantages:** • Few drug-drug interactions • Well-tolerated	**INSTI Class Disadvantages:** • Limited data on pediatric dosing or safety
	BIC	Once-daily administration Can give with or without food Available in FDC tablets (see Appendix A, Table 1)	The FDC tablet **is not recommended** for patients with hepatic impairment or an estimated CrCl <30 mL/min. The FDC tablet **should not be coadministered** with rifampin or dofetilide.
	DTG	Once-daily administration Can give with food Available in FDC tablets (see Appendix A, Table 1) Single-agent DTG pills are available in several doses and are small in size.	Drug interactions with EFV, FPV/r, TPV/r, and rifampin, necessitating twice-daily dosing of DTG CNS side effects, particularly sleep disturbances and possible increased risk of NTDs in infants born to women who were receiving DTG at the time of conception
	EVG	Once-daily administration Available in FDC tablets (see Appendix A, Table 1)	Among INSTIs, EVG has the lowest barrier to the development of resistance. If EVG is coadministered with COBI, there is potential for multiple drug interactions because COBI is metabolized by hepatic enzymes (e.g., CYP3A4). COBI inhibits tubular secretion of creatinine, and this may result in increased serum creatinine but normal glomerular clearance.

Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children (page 2 of 4)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
INSTIs In Alphabetical Order, continued	RAL	Can give with food Available in tablet, chewable tablet, and powder formulations Once-daily administration (with RAL HD) can be used for treatment-naive or virologically suppressed children weighing ≥40 kg.	Potential for rare systemic allergic reaction or hepatitis Granule formulation requires a multistep preparation before administration; caregiver must be taught how to properly prepare this formulation.
NNRTIs In Alphabetical Order	All NNRTIs	**NNRTI Class Advantages:** • Long half-life • Lower risk of dyslipidemia and fat maldistribution than PIs • PI-sparing • Lower pill burden than PIs for children taking the solid formulation; easier to use and adhere to than PI-based regimens	**NNRTI Class Disadvantages:** • A single mutation can confer resistance, with cross-resistance between EFV and NVP. • Rare but serious and potentially life-threatening cases of skin rash, including SJS, and hepatic toxicity. All NNRTIs pose this risk, but the risk is greatest with NVP. • Potential for multiple drug interactions due to metabolism via hepatic enzymes (e.g., CYP3A4)
	EFV	Once-daily administration Available in FDC tablets (see Appendix A, Table 1) Potent ARV activity Can give with food (but avoid high-fat meals) Capsules can be opened and added to food.	Neuropsychiatric AEs (bedtime dosing is recommended to reduce CNS effects) Rash (generally mild) No commercially available liquid formulation Limited data on dosing for children aged <3 years No data on dosing for children aged <3 months
	NVP	Liquid formulation is available. Dosing information for young infants is available. Can give with food Extended-release formulation is available that allows for once-daily dosing in older children.	Reduced virologic efficacy in young infants, regardless of exposure to NVP as part of a peripartum preventive regimen Higher incidence of rash/HSR than other NNRTIs Higher rates of serious hepatic toxicity than EFV Decreased virologic response compared with EFV Twice-daily dosing necessary in children with BSA <0.58 m^2 Low barrier to resistance
	RPV	Once-daily dosing Available in FDC tablets (see Appendix A, Table 1)	Should not use in patients with viral loads >100,000 copies/mL Must be taken with a ≥500 kcal meal at a consistent time each day; this may affect adherence. Low barrier to resistance
PIs In Alphabetical Order	All PIs	**PI Class Advantages:** • NNRTI-sparing • Clinical, virologic, and immunologic efficacy are well-documented. • Resistance to PIs requires multiple mutations. • When combined with a dual-NRTI backbone, a regimen that contains a PI targets HIV at two steps of viral replication by inhibiting the activity of viral reverse transcriptase and protease enzymes.	**PI Class Disadvantages:** • Metabolic complications, including dyslipidemia, fat maldistribution, and insulin resistance • Potential for multiple drug interactions because of metabolism via hepatic enzymes (e.g., CYP3A4) • Higher pill burden than NRTI-based or NNRTI-based regimens for patients taking solid formulations • Poor palatability of liquid preparations, which may affect adherence • Most PIs require RTV boosting, resulting in drug interactions that are associated with RTV

Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children (page 3 of 4)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
PIs In Alphabetical Order, continued	Boosted ATV	Once-daily dosing Powder formulation is available. ATV has less effect on TG and total cholesterol levels than other PIs (but RTV boosting may be associated with elevations in these parameters).	No liquid formulation Should be administered with food Indirect hyperbilirubinemia is common, but asymptomatic. Scleral icterus may be distressing to the patient, which may affect adherence. Must be used with caution in patients with pre-existing conduction system defects (can prolong PR interval of ECG). RTV is associated with a large number of drug interactions.
	Boosted DRV	Can be used once daily in children aged ≥12 years Liquid formulation is available. DRV requires a boosting agent. Available in FDC tablets (see Appendix A, Table 1)	Pediatric pill burden high with current tablet dose formulations Should be administered with food Must be boosted to achieve adequate plasma concentrations Contains sulfa moiety. The potential for cross-sensitivity between DRV and other drugs in sulfonamide class is unknown. RTV is associated with a large number of drug interactions. Can only be used once daily in the absence of certain PI-associated resistance mutations
	LPV/r	LPV is only available coformulated with RTV in liquid and tablet formulations. Tablets can be given without regard to food, but they may be tolerated better when taken with meal or snack.	Poor palatability of liquid formulation (bitter taste). Liquid formulation should be administered with food. RTV is associated with a large number of drug interactions. Should not be administered to neonates before a postmenstrual age of 42 weeks (the span of time between the first day of the mother's last menstrual period and birth, plus the time elapsed after birth) and a postnatal age ≥14 days Must be used with caution in patients with pre-existing conduction system defects (can prolong PR and QT interval of ECG)
Dual-NRTI Backbones In Alphabetical Order	ABC **plus** (3TC **or** FTC)	Palatable liquid formulations Can give with food Available in FDC tablets (see Appendix A, Table 1)	Risk of ABC HSR; perform HLA-B*5701 screening before initiating ABC.
	FTC/TAF for children aged ≥6 years	Once-daily dosing Small tablet size Lower risk of TFV-associated renal and bone toxicity with TAF than with TDF in adults Available in FDC tablets (see Appendix A, Table 1)	Limited data on the safety and efficacy of this combination in children Increased lipid levels

Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children (page 4 of 4)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
Dual-NRTI Backbones In Alphabetical Order, continued	TDF **plus** (3TC **or** FTC) for adolescents with SMRs of 4 or 5	Once-daily dosing for TDF Resistance is slow to develop. Lower risk of mitochondrial toxicity than other NRTIs Can give with food Available as reduced-strength tablets and oral powder for use in younger children Available in FDC tablets (see Appendix A, Table 1)	Limited pediatric experience Potential bone and renal toxicity Appropriate dosing is complicated by numerous drug-drug interactions with other ARV agents, including ddI, LPV/r, ATV, and TPV.
	ZDV **plus** (3TC **or** FTC)	Extensive pediatric experience Coformulations of ZDV and 3TC are available (Combivir and generic) for children weighing ≥30 kg. Palatable liquid formulations Can give with food FTC is available as a palatable liquid formulation that can be administered once daily.	Bone marrow suppression and lipoatrophy with ZDV
	ZDV **plus** ABC	Palatable liquid formulations Can give with food	Risk of ABC HSR; perform HLA-B*5701 screening before initiating ABC. Bone marrow suppression and lipoatrophy with ZDV

Key: 3TC = lamivudine; ABC = abacavir; AE = adverse event; ARV = antiretroviral; ATV = atazanavir; BIC = bictegravir; BSA = body surface area; CNS = central nervous system; COBI = cobicistat; CrCl = creatinine clearance; CYP = cytochrome P450; ddI = didanosine; DRV = darunavir; DTG = dolutegravir; ECG = electrocardiogram; EFV = efavirenz; EVG = elvitegravir; FDC = fixed-dose combination; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; HD = high dose; HSR = hypersensitivity reaction; INSTI = integrase strand transfer inhibitor; LPV = lopinavir; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NTD = neural tube defect; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SJS = Stevens-Johnson Syndrome; SMR = sexual maturity rating; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TFV = tenofovir; TG = triglyceride; TPV = tipranavir; TPV/r = tipranavir/ritonavir; ZDV = zidovudine

Table 9. Antiretroviral Regimens or Components That Are Not Recommended for Initial Treatment of HIV Infection in Children

ARV Regimen or Component	Rationale
Unboosted ATV-containing regimens in children	Reduced exposure
Regimens containing only NRTIs	Inferior virologic efficacy
Regimens containing three drug classes	Potential to induce multiclass resistance Use as an initial regimen in children has not been studied
Regimens containing three NRTIs and one NNRTI	Added cost and complexity outweighs any benefit
Full-dose RTV or use of RTV as the sole PI	GI intolerance Metabolic toxicity
LPV/r dosed once daily	Reduced drug exposure
DOR-based regimens	Insufficient data to recommend
Once-daily DRV-based regimens in children aged ≥3 years to <12 years	Insufficient data to recommend
EFV-based regimens for children aged <3 years	Appropriate dose not determined
ETR-based regimens	Insufficient data to recommend
MVC-based regimens	Insufficient data to recommend
Unboosted DRV	Use without RTV has not been studied
Full-dose, dual-PI regimens	Insufficient data to recommend Potential for added toxicities
TDF-containing regimens in children aged <2 years	Potential bone toxicity Appropriate dose has yet to be determined

Key: ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; DOR = doravirine; DRV = darunavir; EFV = efavirenz; ETR = etravirine; GI = gastrointestinal; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RTV = ritonavir; TDF = tenofovir disoproxil fumarate

Table 10. Antiretroviral Regimens or Components That Are Never Recommended for Treating HIV in Children

ARV Regimens That Are Never Recommended for Use in Children		
Regimen	**Rationale**	**Exceptions**
One ARV Drug Alone (Monotherapy)	Rapid development of resistance Inferior antiviral activity compared to regimens that include ≥3 ARV drugs Monotherapy "holding" regimens are associated with more rapid CD4 count declines than nonsuppressive ART.	Infants with perinatal HIV exposure and negative virologic tests who are receiving 4–6 weeks of ZDV prophylaxis to prevent perinatal transmission of HIV
Two NRTIs Alone	Rapid development of resistance Inferior antiviral activity compared to regimens that include ≥3 ARV drugs	**Not recommended** for initial therapy Some clinicians may opt to continue using two NRTIs alone in patients who achieve virologic goals with this regimen.
TDF plus ABC plus (3TC or FTC) as a Triple-NRTI Regimen	High rate of early viral failure when this triple-NRTI regimen was used as initial therapy in treatment-naive adults	**No exceptions**
ARV Components That Are Never Recommended for Use as Part of an ARV Regimen for Children		
Regimen	**Rationale**	**Exceptions**
Dual-NNRTI Combinations	Enhanced toxicity	**No exceptions**
Dual-NRTI Combination of 3TC plus FTC	Similar resistance profile and no additive benefit	**No exceptions**
NVP as Initial Therapy in Adolescent Girls with CD4 Counts >250 cells/mm^3 or Adolescent Boys with CD4 Counts >400 cells/mm^3	Increased incidence of symptomatic (including serious and potentially fatal) hepatic events in these patient groups	Only if benefit clearly outweighs risk

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; CD4 = CD4 T lymphocyte; FTC = emtricitabine; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

Table 11. Neonatal Antiretroviral Management According to Risk of HIV Infection in the Newborn

Drug selection and dosing considerations are related to the age and gestational age of the newborn. Consultation is available through the National Perinatal HIV Hotline (1-888-448-8765).

Level of Perinatal HIV Transmission Risk	Description	Neonatal ARV Management
Low Risk of Perinatal HIV Transmission	Mothers who received ART during pregnancy with sustained viral suppression (defined as a confirmed HIV RNA level <50 copies/mL) near delivery and no concerns related to adherence	ZDV for 4 weeks
Higher Risk of Perinatal HIV Transmission[a,b]	Mothers who received neither antepartum nor intrapartum ARV drugs Mothers who received only intrapartum ARV drugs Mothers who received antepartum and intrapartum ARV drugs but who have detectable viral loads near delivery, particularly when delivery was vaginal Mothers with acute or primary HIV infection during pregnancy or breastfeeding (in which case, the mother **should discontinue breastfeeding**)[c]	Presumptive HIV therapy using either ZDV, 3TC, and NVP (treatment dose) *or* ZDV, 3TC, and RAL administered from birth up to 6 weeks.[d]
Presumed Newborn HIV Exposure	Mothers with unconfirmed HIV status who have at least one positive HIV test at delivery or postpartum *or* Whose newborns have a positive HIV antibody test	ARV management as described above for newborns with a higher risk of perinatal HIV transmission Infant ARV drugs should be discontinued immediately if supplemental testing confirms that the mother does not have HIV
Newborn with HIV[e]	Positive newborn HIV virologic test/NAT	Three-drug ARV regimen using treatment doses

[a] See text for evidence that supports the use of presumptive HIV therapy and a two-drug ARV prophylaxis regimen.

[b] See Intrapartum Care for guidance on indications for scheduled cesarean delivery and intrapartum IV ZDV to reduce the risk of perinatal HIV transmission for mothers with an elevated viral load at delivery.

[c] Most Panel members would opt to administer presumptive HIV therapy to infants whose mothers had acute HIV during pregnancy because of the higher risk for *in utero* transmission. If acute HIV is diagnosed during breastfeeding, the mother should stop breastfeeding.

[d] The optimal duration of presumptive HIV therapy in newborns who are at a higher risk of perinatal HIV transmission is unknown. If possible, newborns who are at a higher risk of HIV acquisition should receive ZDV for 6 weeks. Additional medications, such as 3TC, RAL, or NVP, may need to administered for 2 to 6 weeks; the recommended durations for these drugs vary based on HIV NAT results, maternal viral load at the time of delivery, and additional risk factors for HIV transmission. Consultation with an expert in pediatric HIV is recommended when selecting a therapy duration, as this decision should be based on case-specific risk factors and interim HIV NAT results. The two-drug regimen used in NICHD-HPTN 040/PACTG 1043 for infants who were at a higher risk of HIV acquisition is described in the text (see the Two-Drug Antiretroviral Prophylaxis section).

[e] Most Panel members do not recommend delaying the initiation of ART pending results of the confirmatory HIV NAT, given the low likelihood of a false-positive HIV NAT.

Note: ARV drugs should be initiated as close to the time of birth as possible, preferably within 6 to 12 hours of delivery. See Table 12 for dosing specifics.

Key: 3TC = lamivudine; ART = antiretroviral therapy; ARV = antiretroviral; IV = intravenous; NAT = nucleic acid test; NVP = nevirapine; the Panel = Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission; RAL = raltegravir; ZDV = zidovudine

Table 12. Antiretroviral Dosing Recommendations for Newborns (page 1 of 3)

Newborns at Low Risk of Perinatal HIV Transmission	
Recommended Regimen	**Recommended Duration**
ZDV	ZDV administered for 4 weeks at the doses listed below
Newborns at Higher Risk of Perinatal HIV Transmission	
Recommended Regimen	**Recommended Duration**
Three-drug HIV therapy: ZDV plus 3TC plus (NVP *or* RAL)	ZDV administered for 6 weeks, with no increase to the 12 mg/kg dose unless the infant has confirmed HIV infection. Dosing for 3TC, NVP, and RAL is described below. Duration for these three drugs may vary; see the guidance in footnote.[a]
Newborns with HIV Infection	
Recommended Regimen	**Lifelong Duration Recommended**[b]
Three-drug HIV therapy: ZDV plus 3TC plus (NVP *or* RAL)	Lifelong therapy in accordance with current treatment guidelines. The ARV regimen should be individualized based on the infant's age and clinical determinants. NVP can be replaced with LPV/r when the infant reaches a postmenstrual age of ≥42 weeks (defined as the time from the first day of the mother's last menstrual period to birth plus the time elapsed after birth) and a postnatal age ≥14 days. NVP can be replaced with RAL at any age in infants who were born at a postmenstrual age of ≥37 weeks and who weigh ≥2 kg.

Drug	Drug Doses by Gestational Age at Birth
ZDV **Note:** For newborns who are unable to tolerate oral agents, the IV dose is 75% of the oral dose while maintaining the same dosing interval.	**≥35 Weeks Gestation at Birth** *Birth to Age 4 Weeks:* • ZDV 4 mg/kg per dose orally twice daily *Age >4 Weeks:* • ZDV 12 mg/kg per dose orally twice daily; only make this dose increase for infants with confirmed HIV infection. **Simplified Weight-Band Dosing for Newborns Aged ≥35 Weeks Gestation from Birth to 4 Weeks** Weight Band: 2 to <3 kg — Volume of ZDV 10 mg/mL Oral Syrup Twice Daily: 1 mL Weight Band: 3 to <4 kg — Volume of ZDV 10 mg/mL Oral Syrup Twice Daily: 1.5 mL Weight Band: 4 to <5 kg — Volume of ZDV 10 mg/mL Oral Syrup Twice Daily: 2 mL
	≥30 to <35 Weeks Gestation at Birth *Birth to Age 2 Weeks:* • ZDV 2 mg/kg per dose orally twice daily *Age 2 Weeks to 6 to 8 Weeks:* • ZDV 3 mg/kg per dose orally twice daily *Age >6 to 8 Weeks:* • ZDV 12 mg/kg per dose orally twice daily; only make this dose increase for infants with confirmed HIV infection.
	<30 Weeks Gestation at Birth *Birth to Age 4 Weeks:* • ZDV 2 mg/kg per dose orally twice daily *Age 4 to 8–10 Weeks:* • ZDV 3 mg/kg per dose orally twice daily *Age >8 to 10 Weeks:* • ZDV 12 mg/kg per dose orally twice daily; only make this dose increase for infants with confirmed HIV infection
3TC	**≥32 Weeks Gestation at Birth** *Birth to Age 4 Weeks:* • 3TC 2 mg/kg per dose orally twice daily *Age >4 Weeks:* • 3TC 4 mg/kg per dose orally twice daily

Table 12. Antiretroviral Dosing Recommendations for Newborns (page 2 of 3)

<table>
<tr><th>Drug</th><th>Drug Doses by Gestational Age at Birth</th></tr>
<tr><td>NVP</td><td>≥37 Weeks Gestation at Birth
Birth to Age 4 Weeks:
• NVP 6 mg/kg per dose orally twice daily[c]
Age >4 Weeks:
• NVP 200 mg/m^2 of BSA per dose orally twice daily; only make this dose increase for infants with confirmed HIV infection.</td></tr>
<tr><td></td><td>≥34 to <37 Weeks Gestation at Birth
Birth to Age 1 Week:
• NVP 4 mg/kg per dose orally twice daily
Age 1 to 4 Weeks:
• NVP 6 mg/kg per dose orally twice daily
Age >4 Weeks:
• NVP 200 mg/m^2 of BSA per dose orally twice daily; only make this dose increase for infants with confirmed HIV infection.</td></tr>
<tr><td>RAL

Note: If the mother has taken RAL 2–24 hours prior to delivery, the neonate's first dose of RAL should be delayed until 24–48 hours after birth; additional ARV drugs should be started as soon as possible.[7]</td><td>≥37 Weeks Gestation at Birth and Weighing ≥2 kg[d]
Birth to Age 6 Weeks:
<table>
<tr><th>Body Weight</th><th>Volume (Dose) of RAL 10 mg/mL Suspension</th></tr>
<tr><td>Birth to 1 Week: Once-Daily Dosing</td><td>Approximately 1.5 mg/kg per dose</td></tr>
<tr><td>2 to <3 kg</td><td>0.4 mL (4 mg) once daily</td></tr>
<tr><td>3 to <4 kg</td><td>0.5 mL (5 mg) once daily</td></tr>
<tr><td>4 to <5 kg</td><td>0.7 mL (7 mg) once daily</td></tr>
<tr><td>1 to 4 Weeks: Twice-Daily Dosing</td><td>Approximately 3 mg/kg per dose</td></tr>
<tr><td>2 to <3 kg</td><td>0.8 mL (8 mg) twice daily</td></tr>
<tr><td>3 to <4 kg</td><td>1 mL (10 mg) twice daily</td></tr>
<tr><td>4 to <5 kg</td><td>1.5 mL (15 mg) twice daily</td></tr>
<tr><td>4 to 6 Weeks: Twice-Daily Dosing</td><td>Approximately 6 mg/kg per dose</td></tr>
<tr><td>3 to <4 kg</td><td>2.5 mL (25 mg) twice daily</td></tr>
<tr><td>4 to <6 kg</td><td>3 mL (30 mg) twice daily</td></tr>
<tr><td>6 to <8 kg</td><td>4 mL (40 mg) twice daily</td></tr>
</table></td></tr>
</table>

[a] The optimal duration of presumptive HIV therapy in newborns who are at a higher risk of perinatal HIV transmission is unknown. If possible, newborns who are at a higher risk of HIV acquisition should receive ZDV for 6 weeks. Additional medications, such as 3TC, RAL, or NVP, may need to administered for 2 to 6 weeks; the recommended durations for these drugs vary based on HIV NAT results, maternal viral load at the time of delivery, and additional risk factors for HIV transmission. Consultation with an expert in pediatric HIV is recommended when selecting a therapy duration, as this decision should be based on case-specific risk factors and interim HIV NAT results. The two-drug regimen used in NICHD-HPTN 040/PACTG 1043 for infants who were at a higher risk of HIV acquisition is described in the text (see the Two-Drug Antiretroviral Prophylaxis section).

[b] For ARV management after the newborn period, see the Pediatric Antiretroviral Guidelines.

[c] This dose is an investigational NVP treatment dose recommended by the Panel; the FDA has not approved a dose of NVP for infants aged <1 month. See the Two-Drug Antiretroviral Prophylaxis section for prophylactic NVP dosing if using the NICHD-HPTN 040/PACTG 1043 prophylaxis regimen.

[d] RAL dosing is increased at 1 and 4 weeks of age because metabolism by UGT1A1 is low at birth and increases rapidly during the next 4–6 weeks of life. No dosing information is available for preterm infants or infants weighing <2 kg at birth.

Key: 3TC = lamivudine; ARV =antiretroviral; BSA = body surface area; FDA = Food and Drug Administration; IV = intravenous; LPV/r = lopinavir/ritonavir; NAT = nucleic acid test; NVP = nevirapine; the Panel = the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission; RAL = raltegravir; UGT = uridine diphosphate glucotransferase; ZDV = zidovudine

Table 13. Approaches for Monitoring Medication Adherence

Routine Assessment of Medication Adherence in Clinical Care[a]	Description
Monitor viral load.	Viral load monitoring should be done more frequently after initiating or changing medications.[a]
Assess a quantitative self-report of missed doses.	Ask the patient and/or caregiver about the number of missed doses over a defined period (1, 3, or 7 days).
Request a description of the medication regimen.	Ask the patient and/or caregiver about the name, appearance, and number of medications, and how often the medications are taken.
Assess barriers to medication administration.	Engage the patient and caregiver in a dialogue about potential barriers to adherence and strategies to overcome them.
Monitor pharmacy refills.	Approaches include a pharmacy-based or clinic-based assessment of on-time medication refills.
Conduct announced and unannounced pill counts.	Approaches include asking patients to bring medications to the clinic, home visits, or referral to community health nursing.
Targeted Approaches to Monitoring Adherence in Special Circumstances	**Description**
Implement DOT.	Include a brief period of hospitalization if indicated.
Measure drug concentration in plasma or DBS.	Measuring drug concentrations can be considered for particular drugs.
Approaches to Monitoring Medication Adherence in Research Settings	**Description**
Measure drug concentrations in hair.	Measuring hair drug concentrations can be considered for particular drugs; it provides a good measure of adherence over time.[17,45,46]
Use electronic monitoring devices.	Approaches include MEMS caps and Wisepill.
Use cell phone-based technologies.	Approaches include interactive voice response, text messaging, and mobile apps.

[a] See Clinical and Laboratory Monitoring of Pediatric HIV Infection regarding the frequency of adherence assessment after initiating or changing therapy.

Key: apps = applications; DBS = dried blood spots; DOT = directly observed therapy; MEMS = Medication Event Monitoring System

Table 14. Strategies to Improve Adherence to Antiretroviral Medications

Initial Intervention Strategies
• Establish trust and identify mutually acceptable goals for care.
• Obtain explicit agreement on the need for treatment and adherence.
• Identify depression, low self-esteem, substance abuse, or other mental health issues in the child/adolescent and/or the caregiver that may affect adherence. Evaluate and initiate treatment for mental health issues before starting ARV drugs, if possible.
• Determine whether the child is aware of their HIV status. Consider talking to the child's caregivers about disclosing this information to the child in a developmentally appropriate way.
• Identify family, friends, health team members, and others who can support adherence.
• Educate the patient and family about the critical role of adherence in therapy outcome, including the relationship between partial adherence and resistance and the potential impact on future drug regimen choices. Develop a treatment plan that the patient and family understand and to which they feel committed.
• Work with the patient and family to make specific plans for taking medications as prescribed and for supporting adherence. Assist them in arranging administration during day care, school, and in other settings, when needed. Consider home delivery of medications.
• Establish a patient's readiness to take medication by staging practice sessions or by other means.
• Schedule a home visit to review medications and determine how they will be administered in the home setting.
• In certain circumstances, consider a brief period of hospitalization at the start of therapy for patient education and to assess the tolerability of the chosen medications.
Medication Strategies
• Choose the simplest regimen possible; reduce dosing frequency, pill size, and number of pills (see Appendix A, Table 1 and Appendix A, Table 2).
• When choosing a regimen, consider the patient's daily and weekly routines and potential variations in patient and family activities.
• Choose the most palatable medicine possible (pharmacists may be able to add syrups or flavoring agents to increase palatability).
• Choose drugs with the fewest AEs; provide anticipatory guidance for managing AEs.
• Simplify food requirements for medication administration.
• Prescribe drugs carefully to avoid adverse drug-drug interactions.
• Assess pill-swallowing capacity and offer pill-swallowing training and aids (e.g., pill-swallowing cup, pill glide). Adjust pill size as needed.
Follow-Up Intervention Strategies
• Have more than one member of the multidisciplinary team monitor adherence at each visit and in between visits by telephone, email, text, and social media, as needed.
• Provide ongoing support, encouragement, and understanding of the difficulties associated with maintaining adherence to daily medication regimens.
• Use patient education aids, including pictures, calendars, and stickers.
• Encourage the use of pill boxes, reminders, mobile apps, alarms, and timers.
• Provide follow-up clinic visits, telephone calls, and text messages to support and assess adherence.
• Provide access to support groups, peer groups, or one-on-one counseling for caregivers and patients, especially for those with known depression or drug use issues that are known to decrease adherence.
• Provide pharmacist-based adherence support, such as medication education and counseling, blister packs, refill reminders, automatic refills, and home delivery of medications.
• Consider DOT at home, in the clinic, or, in certain circumstances, during a brief period of inpatient hospitalization.
• Consider gastrostomy tube use in certain circumstances.
• Information on other interventions to consider can be found at the Complete Listing of Medication Adherence Evidence-Based Behavioral Interventions on CDC's website.
• Consult the CDC Every Dose Every Day toolkit.

Key: apps = applications; ARV = antiretroviral; AE = adverse effect; CDC = Centers for Disease Control and Prevention; DOT = directly observed therapy

Table 15a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity (Last updated April 14, 2020; last reviewed April 14, 2020) (page 1 of 4)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Global CNS Depression	LPV/r oral solution (contains both ethanol and propylene glycol as excipients)	**Onset:** • 1–6 days after starting LPV/r **Presentation** *Neonates/Premature Infants:* • Global CNS depression (e.g., abnormal EEG, altered state of consciousness, somnolence)	Unknown; rare case reports have been published	Prematurity Low birth weight Aged <14 days (whether birth was premature or term)	Avoid use of LPV/r until a postmenstrual age of 42 weeks and a postnatal age of ≥14 days unless no other alternatives are available, see Lopinavir/Ritonavir.	Discontinue LPV/r; symptoms should resolve in 1–5 days. If needed, reintroduction of LPV/r can be considered once the patient is outside the vulnerable period (i.e., postmenstrual age of 42 weeks and a postnatal age ≥14 days).
Neuropsychiatric Symptoms and Other CNS Manifestations	EFV	**Onset:** • For many symptoms, onset is 1–2 days after starting EFV. • Many symptoms subside or diminish by 2–4 weeks, but symptoms may persist in a significant proportion of patients. **Presentation (May Include One or More of the Following)** *Neuropsychiatric Symptoms:* • Abnormal dreams • Psychosis • Suicidal ideation or attempted/ completed suicide *Other CNS Manifestations:* • Dizziness • Somnolence • Insomnia or poor sleep quality • Impaired concentration • Seizures (including absence seizures) • Cerebellar dysfunction (e.g., tremor, dysmetria, ataxia) **Note:** CNS side effects (e.g., impaired concentration, abnormal dreams, sleep disturbances) may be more difficult to assess in children.	Variable, depending on age, symptoms, and assessment method **Children:** • 24% of patients experienced any EFV-related CNS manifestation in one case series, with 18% of participants requiring drug discontinuation. • Five of 45 participants (11%) experienced new-onset seizures in one study of children aged <36 months; two of these participants had alternative causes for seizures. • Cases of cerebellar dysfunction have been reported in children with very high EFV plasma levels. **Adults:** • 30% incidence for any CNS manifestations of any severity. • 6% incidence for EFV-related, severe CNS manifestations, including suicidality. However, evidence is conflicting about whether EFV use increases the incidence of suicidality. • One case series reported 20 women with ataxia that resolved upon EFV discontinuation, but frequency was not reported.	Insomnia is associated with elevated EFV trough concentration (≥4 mcg/mL) CYP2B6 polymorphisms that decrease EFV metabolism and cause increased EFV serum concentrations (CYP2B6 516 T/T genotype or co-carriage of CYP2B6 516 G/T and 983 T/C variants) History of psychiatric illness or use of psychoactive drugs	Administer EFV on an empty stomach, preferably at bedtime. Prescreen for psychiatric illness; avoid use in the presence of psychiatric illness, including depression or suicidal thoughts. Avoid concomitant use of psychoactive drugs. Consider using TDM in children with mild or moderate EFV-associated toxicities.	If symptoms are excessive or persistent, obtain EFV trough concentration. If EFV trough concentration is >4 mcg/mL and/or symptoms are severe, strongly consider drug substitution if a suitable alternative exists. Alternatively, consider dose reduction with repeat TDM and dose adjustment (with input from an expert pharmacologist).

Table 15a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity (Last updated April 14, 2020; last reviewed April 14, 2020) (page 2 of 4)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Neuropsychiatric Symptoms and Other CNS Manifestations, continued	RPV	**Onset:** • Most symptoms occur in the first 4–8 weeks of treatment. **Presentation** *Neuropsychiatric Symptoms:* • Depressive disorders • Suicidal ideation • Abnormal dreams/nightmares *Other CNS Manifestations:* • Headache • Dizziness • Insomnia • Somnolence	**Adults:** • CNS/neuro-psychiatric adverse events of all severity grades were reported in 43% of patients at 96 weeks (most were Grade 1). Depressive disorders of all severity grades were reported in 9% of patients; 1% of patients discontinued RPV due to severe depressive disorders. **Children:** • Depressive disorders of all severity grades were reported in 19.4% of pediatric patients aged 12–17 years. Severe depressive disorders were reported in 5.6% of patients, including one suicide attempt. • Somnolence was reported in five of 36 children (14%).	History of neuropsychiatric illness	Monitor carefully for depressive disorders and other CNS symptoms.	Consider drug substitution in cases of severe symptoms.
	RAL	**Onset:** • As early as 3–4 days after starting RAL **Presentation:** • Increased psychomotor activity • Headaches • Insomnia • Depression • Cerebellar dysfunction (e.g., tremor, dysarthria, ataxia)	**Children:** • Increased psychomotor activity was reported in one child. **Adults:** • Headache • Insomnia (<5% in adult trials) • Rare case reports of cerebellar dysfunction in adults	Elevated RAL concentrations Co-treatment with TDF, a PPI, or inhibitors of UGT1A1 Prior history of insomnia or depression	Prescreen for psychiatric symptoms. Monitor carefully for CNS symptoms. Use with caution in the presence of drugs that increase RAL concentration.	Consider drug substitution (RAL or coadministered drug) in cases of severe insomnia or other neuropsychiatric symptoms.

Table 15a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity (Last updated April 14, 2020; last reviewed April 14, 2020) (page 3 of 4)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Neuropsychiatric Symptoms and Other CNS Manifestations, continued	DTG	**Onset:** • 7–30 days after starting DTG **Presentation** *Neuropsychiatric Symptoms:* • Depression or exacerbation of preexisting depression • Anxiety • Suicidal ideation or attempted/ completed suicide • Drowsiness • Neurocognitive deficits (lower total competence and school performance) *Other CNS Manifestations (Generally Mild):* • Sleep disturbances • Dizziness • Headache	**Children:** • In a retrospective cohort analysis, neuropsychiatric events that resulted in discontinuation occurred in two of 29 (6.8%) children who initiated DTG. **Adults:** • 2.7% of the neuropsychiatric AEs reported in a large prospective cohort resulted in treatment discontinuation. • Higher frequency of neuropsychiatric symptoms reported with DTG than with other INSTIs. A class effect has been suggested.	Pre-existing depression or other psychiatric illness History of ARV-related neuropsychiatric symptoms Higher frequency of neuropsychiatric symptoms reported when DTG is coadministered with ABC; however, evidence is conflicting. UGT1A1*6 and/or *28 polymorphism (reported in patients of Asian descent)	Use with caution in the presence of psychiatric illness, especially in patients with depression or a history of ARV-related neuropsychiatric symptoms. Consider morning dosing of DTG.	For persistent or severe neuropsychiatric symptoms, consider discontinuing DTG if a suitable alternative exists. For mild symptoms, continue DTG and counsel patient that symptoms will likely resolve with time.

Table 15a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity (Last updated April 14, 2020; last reviewed April 14, 2020) (page 4 of 4)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Neuropsychiatric Symptoms and Other CNS Manifestations, continued	BIC	**Onset:** • 1–63 days after starting BIC (as late as 233 days for schizoaffective disorders) **Presentation** *Neuropsychiatric Symptoms:* • Depression or exacerbation of pre-existing depression • Suicidal ideation or attempted suicide • Schizoaffective disorders • Anxiety *Other CNS Manifestations (Generally Mild):* • Abnormal dreams • Dizziness • Insomnia	Data in children and adults come mostly from clinical trials. Overall, the frequency of neuropsychiatric events in BIC and DTG comparator arms appeared similar in adult clinical trials. **Children:** • 1 child (1%) had Grade 2 insomnia and anxiety that led to drug discontinuation. **Adults:** • Abnormal dreams, dizziness, and insomnia occurred in 1% to 5% of adults. • Suicidal ideation, suicide attempts, schizoaffective disorders, and depression occurred in <1% of adults.	Pre-existing depression or other psychiatric conditions History of ARV-related neuropsychiatric symptoms	Use with caution in the presence of psychiatric conditions, or in patients with a history of ARV-related neuropsychiatric symptoms.	For persistent or severe neuropsychiatric symptoms, consider discontinuing BIC if a suitable alternative exists. For mild symptoms, continue BIC and counsel patient that symptoms will likely resolve with time.

Key: ABC = abacavir; ARV = antiretroviral; BIC = bictegravir; CNS = central nervous system; CYP = cytochrome P; DTG = dolutegravir; EEG = electroencephalogram; EFV = efavirenz; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; PPI = proton pump inhibitor; RAL = raltegravir; RPV = rilpivirine; TDF = tenofovir disoproxil fumarate; TDM = therapeutic drug monitoring; UGT = uridine diphosphate-glucuronosyltransferase

Table 15b. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Dyslipidemia (Last updated April 14, 2020; last reviewed April 14, 2020) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Dyslipidemia	**PIs:** • All PIs, especially RTV-boosted PIs; lower incidence reported with DRV/r and ATV, with or without RTV. **NRTIs:** • Lower incidence reported with TDF than with TAF. **NNRTIs:** • Lower incidence reported with NVP, RPV, and ETR than with EFV.	**Onset:** • As early as 2 weeks to months after beginning therapy **Presentation** *PIs:* • ↑ LDL-C, TC, and TG *NRTIs:* • ↑ LDL-C, TC, and TG *NNRTIs:* • ↑ LDL-C, TC, and HDL-C	Reported frequency varies with specific ARV regimen, duration of ART, and the specific laboratory parameters used to diagnose lipid abnormalities. 10% to 20% of young children receiving LPV/r will have lipid abnormalities. 40% to 75% of older children and adolescents with prolonged ART history will have lipid abnormalities. Higher abnormal fasting serum lipids have been observed in ART-naive adults who received EVG/c/FTC/TAF than in those who received EVG/c/FTC/TDF. Increase in serum lipids from baseline has also been noted in adolescents receiving EVG/c/FTC/TAF.	Advanced-stage HIV disease High-fat, high-cholesterol diet Lack of exercise Obesity Hypertension Smoking Family history of dyslipidemia or premature ASCVD Metabolic syndrome Fat maldistribution	**Prevention:** • Low-fat diet • Exercise • Smoking-prevention counseling • When possible, use ARVs associated with a lower prevalence of dyslipidemia. These include INSTIs and newer PIs (e.g., ATV, DRV). **Monitoring**[a] *Adolescents and Adults:* • Obtain FLP (TC, HDL-C, non-HDL-C, LDL-C, and TG) twice (>2 weeks but ≤3 months apart, average these results) Monitor FLP every 6 months (for abnormal results) or every 12 months (for normal results). *Children (Aged ≥2 Years) without Lipid Abnormalities or Additional Risk Factors:* • Obtain nonfasting screening lipid profiles at entry into care and then every 6–12 months, depending on the results. • If TG or LDL-C is elevated or if a patient has additional risk factors, obtain FLP. *Children with Lipid Abnormalities and/or Additional Risk Factors:* • Obtain 12-hour FLP before initiating or changing therapy and every 6 months thereafter (more often if indicated). *Children Receiving Lipid-Lowering Therapy with Statins or Fibrates:* • Obtain 12-hour FLP, LFT, and CK at 4 weeks, 8 weeks, and 3 months after starting lipid therapy.	Assess all patients for additional ASCVD risk factors. Patients with HIV are considered to be at moderate risk of ASCVD.[b] ARV regimen changes should be considered, especially when the patient is receiving older PIs (e.g., LPV/r) and/or RTV boosting. Switching to a PI-sparing regimen, a PI-based regimen with a more favorable lipid profile, or COBI boosting causes a decline in LDL-C or TG values. However, the lipid-lowering effect for LDL-C is less pronounced than with statin therapy. Refer patients to a lipid specialist early if LDL-C is ≥250 mg/dL or TG is ≥500 mg/dL. If LDL-C is ≥130 mg/dL but <250 mg, or TG is ≥150 mg/dL but <500 mg/dL, the following staged treatment approach is recommended by the NHLBI guidelines:[b] • Implement diet, nutrition, and lifestyle management for 6–9 months. Consult with a dietician if one is available. • If a 6-month to 9-month trial of lifestyle modification fails and the patient is aged ≥10 years, consider implementing lipid-lowering therapy after consulting a lipid specialist. • Statin therapy should be considered for patients with elevated LDL-C levels. NHLBI provides recommendations for statin therapy in patients with specific LDL-C levels and risk factors.[b]

Table 15b. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Dyslipidemia (Last updated April 14, 2020; last reviewed April 14, 2020) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Dyslipidemia, continued					• If there are minimal alterations in AST, ALT, and CK, monitor every 3–4 months during the first year and every 6 months thereafter (or as clinically indicated). • Repeat FLP 4 weeks after increasing doses of antihyperlipidemic agents.	• Drug therapy can be considered in cases of severe hypertriglyceridemia (TG ≥500 mg/dL). Fibrates (gemfibrozil and fenofibrate) and N-3 PUFAs derived from fish oils may be used. The long-term risks of lipid abnormalities in children who are receiving ART are unclear. However, persistent dyslipidemia in children may lead to premature ASCVD.

[a] Given the burden of collecting fasting blood samples, some practitioners routinely measure cholesterol and TG from nonfasting blood samples and follow up abnormal values with a test done in the fasted state.

[b] Refer to the NHLBI guidelines: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents.

Key: ALT = alanine aminotransferase; ART = antiretroviral therapy; ARV = antiretroviral; ASCVD = atherosclerotic cardiovascular disease; AST = aspartate aminotransferase; ATV = atazanavir; CK = creatine kinase; COBI = cobicistat; DRV = darunavir; DRV/r = darunavir/ritonavir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; FLP = fasting lipid profile; FTC = emtricitabine; HDL-C = high-density lipoprotein cholesterol; INSTI = integrase strand transfer inhibitor; LDL-C = low-density lipoprotein cholesterol; LFT = liver function test; LPV/r = lopinavir/ritonavir; NHLBI = National Heart, Lung, and Blood Institute; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PUFA = polyunsaturated fatty acid; RPV = rilpivirine; RTV = ritonavir; TAF = tenofovir alafenamide; TC = total cholesterol; TDF = tenofovir disoproxil fumarate; TG = triglycerides

Table 15c. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Gastrointestinal Effects (Last updated April 16, 2019; last reviewed April 14, 2020) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Nausea/Vomiting	All ARV drugs, but most notably RTV-boosted PIs	**Onset:** • Early **Presentation:** • Nausea and emesis, both of which may be associated with anorexia and/or abdominal pain	Varies by ARV agent; generally <15%	Unknown	Instruct patient to take PIs with food. Monitor for weight loss and ARV adherence.	Reassure patient that these adverse effects generally improve over time (usually in 6–8 weeks). Consider switching to ARV drugs with smaller tablet sizes (see Appendix A, Table 2). Provide supportive care. In extreme or persistent cases, use antiemetics or switch to another ARV regimen.
Diarrhea	All ARV drugs, but most notably RTV-boosted PIs	**Onset:** • Early **Presentation:** • More frequent bowel movements and stools that are generally soft	Varies by ARV agent; generally <15%	Unknown	Monitor for weight loss and dehydration.	In prolonged or severe cases, exclude infectious or noninfectious (e.g., lactose intolerance) causes of diarrhea. Reassure patient that this adverse effect generally improves over time (usually in 6–8 weeks). Consider switching to another ARV regimen in persistent and severe cases. Treatment data in children are lacking; however, the following strategies may be useful when the ARV regimen cannot be changed: • Dietary modification • Using bulk-forming agents (e.g., psyllium) • Using antimotility agents (e.g., loperamide) • Using crofelemer, which is approved by the FDA to treat ART-associated diarrhea in adults aged ≥18 years; no pediatric data are available.

Table 15c. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Gastrointestinal Effects (Last updated April 16, 2019; last reviewed April 14, 2020) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Pancreatitis	Rare, but may occur with NRTIs or RTV-boosted PIs	**Onset:** • Any time, usually after months of therapy **Presentation:** • Emesis, abdominal pain, elevated amylase and lipase levels (asymptomatic hyperamylasemia or elevated lipase do not in and of themselves indicate pancreatitis)	<2% in a recent case series	Use of concomitant medications that are associated with pancreatitis (e.g., TMP-SMX, pentamidine, ribavirin) Hypertriglyceridemia Advanced HIV infection Previous episode of pancreatitis Alcohol use	Measure serum amylase and lipase concentrations if persistent abdominal pain develops.	Discontinue offending agent and **avoid reintroduction**. Manage symptoms of acute episodes. If pancreatitis is associated with hypertriglyceridemia, consider using interventions to lower TG levels.

Key: ART = antiretroviral therapy; ARV = antiretroviral; FDA = Food and Drug Administration; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RTV = ritonavir; TG = triglyceride; TMP-SMX = trimethoprim sulfamethoxazole

Table 15d. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hematologic Effects (Last updated April 14, 2020; last reviewed April 14, 2020) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Anemia[a]	ZDV	**Onset:** • Variable; weeks to months after starting therapy **Presentation** *More Common:* • Asymptomatic • Mild fatigue • Pallor • Tachypnea *Rare:* • Congestive heart failure	**Newborns Exposed to HIV:** • Severe anemia is uncommon, but may be seen coincident with physiologic Hgb nadir. **Children with HIV Who Are Taking ARV Drugs:** • Anemia is two to three times more common with ZDV-containing regimens than with all other regimens.	**Newborns Exposed to HIV:** • Premature birth is the most common risk factor • *In utero* exposure to ZDV-containing regimens • Advanced maternal HIV • Neonatal blood loss • Combination ARV prophylaxis or presumptive HIV therapy, particularly ZDV plus 3TC **Children with HIV Who Are Taking ARV Drugs:** • Underlying hemoglobinopathy (e.g., sickle cell disease, G6PD deficiency) • Myelosuppressive drugs (e.g., TMP-SMX, rifabutin) • Iron deficiency • Advanced or poorly controlled HIV disease • OIs of the bone marrow • Malnutrition	**Newborns Exposed to HIV:** • Obtain CBC at birth. • Consider repeating CBC at 4 weeks for neonates who are at higher risk (e.g., those born prematurely or who are known to have low birth Hgb) and for neonates who receive ZDV beyond 4 weeks. **Children with HIV Who Are Taking ARV Drugs:** • Avoid using ZDV in children with severe anemia when alternative agents are available. • Obtain CBC as part of routine care (see Clinical and Laboratory Monitoring of Pediatric HIV Infection).	**Newborns Exposed to HIV:** • Anemia rarely requires intervention unless it is symptomatic or Hgb <7.0 g/dL. • ZDV administration can be limited to 4 weeks in low-risk neonates (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection). **Children with HIV Who Are Taking ARV Drugs:** • Discontinue non-ARV, marrow-toxic drugs, if feasible. • Treat coexisting iron deficiency, OIs, and malignancies. • For persistent, severe anemia that is thought to be associated with ARV drugs (typically macrocytic anemia), switch to a regimen that does not contain ZDV.
Macrocytosis	ZDV	**Onset:** • Within days or weeks of starting therapy **Presentation:** • Asymptomatic, but MCV is often >100 fL • Sometimes associated with anemia	>90% to 95% for all ages	None	No monitoring required—macrocytosis can be detected if CBC is obtained as part of routine care (see Clinical and Laboratory Monitoring of Pediatric HIV Infection).	No management required.

Table 15d. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hematologic Effects (Last updated April 14, 2020; last reviewed April 14, 2020) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Neutropenia[a]	ZDV	**Onset:** • Variable **Presentation:** • Asymptomatic	**Newborns Exposed to HIV:** • Rare **Children with HIV Who Are Taking ARV Drugs:** • 2% to 4% of children on ARV drugs • Highest rates occur in children on ZDV-containing regimens	**Newborns Exposed to HIV:** • *In utero* exposure to ARV drugs • Combination ARV prophylaxis, particularly ZDV plus 3TC **Children with HIV Who Are Taking ARV Drugs:** • Advanced or poorly controlled HIV infection • Myelosuppressive drugs (e.g., TMP-SMX, ganciclovir, hydroxyurea, rifabutin)	**Children with HIV Who Are Taking ARV Drugs:** • Obtain CBC as part of routine care.	**Newborns Exposed to HIV:** • No established threshold for intervention; some experts would consider using an alternative NRTI for prophylaxis if ANC reaches <500 cells/mm^3. ZDV administration can be limited to 4 weeks in low-risk neonates (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection). **Children with HIV Who Are Taking ARV Drugs:** • Discontinue non-ARV, marrow-toxic drugs, if feasible. • Treat coexisting OIs and malignancies. • In cases of persistent, severe neutropenia that is thought to be associated with ARV drugs, switch to a regimen that does not contain ZDV.

[a] HIV infection itself, OIs, and medications that are used to prevent OIs (e.g., TMP-SMX) may all contribute to anemia and neutropenia.

Key: 3TC = lamivudine; ANC = absolute neutrophil count; ARV = antiretroviral; CBC = complete blood count; dL = deciliter; fL = femtoliter; G6PD = glucose-6-phosphate dehydrogenase; Hgb = hemoglobin; MCV = mean cell volume; NRTI = nucleoside reverse transcriptase inhibitor; OI = opportunistic infection; TMP-SMX = trimethoprim-sulfamethoxazole; ZDV = zidovudine

Table 15e. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hepatic Events

(Last updated April 14, 2020; last reviewed April 14, 2020) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Hepatitis	Most ARV drugs have been associated with hepatitis, but there is a strong association between hepatitis and the use of NVP and EFV. NVP, EFV, ABC, RAL, DTG, and MVC have been associated with hepatitis in the context of HSRs. NRTIs, especially ZDV, have been associated with lactic acidosis and hepatic steatosis.	**Onset:** • Acute toxic hepatitis most commonly occurs within the first few months of therapy, but it can occur later. • Steatosis presents after months or years of therapy. • Patients with HBV coinfection may experience a hepatitis flare with the initiation or withdrawal of 3TC, FTC, TDF, or TAF. Flare may also occur with the emergence of resistance to 3TC or FTC (especially if the patient is receiving only one anti-HBV agent). Note that TDF and TAF have high barriers to resistance when used to treat HBV. • Hepatitis may be a manifestation of IRIS if it occurs early in therapy, especially in patients with HBV or HCV coinfection. **Presentation:** • Asymptomatic elevation of AST and ALT levels • Symptomatic hepatitis with nausea, fatigue, and jaundice • Hepatitis may present in the context of HSR with rash, lactic acidosis, and hepatic steatosis.	Uncommon	HBV or HCV coinfection Underlying liver disease Use of other hepatotoxic medications and supplements (e.g., St. John's wort [*Hypericum perforatum*], chaparral [*Larrea tridentata*], germander [*Teucrium chamaedrys*]) Alcohol use Pregnancy Obesity Higher drug concentrations of PIs **For NVP-Associated Hepatic Events in Adults:** • Female sex with pre-NVP CD4 count >250 cells/mm^3 • Male sex with pre-NVP CD4 count >400 cells/mm^3 • Population- specific HLA types[a]	**Prevention:** • Avoid concomitant use of hepatotoxic medications. • In patients with elevated levels of hepatic enzymes (>5 times to 10 times ULN) or chronic liver disease, most clinicians would avoid NVP. **Monitoring** *For ARV Drugs Other Than NVP:* • Obtain AST and ALT levels at baseline and at least every 3–4 months thereafter;[b] monitor at-risk patients more frequently (e.g., those with HBV or HCV coinfection or elevated baseline AST and ALT levels). *For NVP:* • Obtain AST and ALT levels at baseline, at 2 weeks, 4 weeks, and then every 3 months.	Evaluate the patient for other infectious and non-infectious causes of hepatitis and monitor the patient closely. **Asymptomatic Hepatitis:** • Potentially offending ARV drugs should be discontinued if ALT or AST level is >5 times ULN. **Symptomatic Hepatitis:** • Discontinue all ARV drugs and other potentially hepatotoxic drugs. • If a patient experiences hepatitis that is attributed to NVP, NVP **should be permanently discontinued**. • Consider viral causes of hepatitis: HAV, HBV, HCV, EBV, and CMV.

Table 15e. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hepatic Events

(Last updated April 14, 2020; last reviewed April 14, 2020) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Indirect Hyperbilirubinemia	ATV	**Onset:** • Within the first months of therapy **Presentation:** • May be asymptomatic or associated with jaundice • Levels of direct bilirubin may be normal or slightly elevated when levels of indirect bilirubin are very high. • Normal AST and ALT	In long-term follow-up, 9% of children who were receiving ATV had at least one total bilirubin level >5 times ULN and 1.4% of children experienced jaundice.	None established.	**Monitoring:** • No ongoing monitoring needed. • After an initial rise over the first few months of therapy, unconjugated bilirubin levels generally stabilize; levels may improve over time.	Isolated indirect hyperbilirubinemia is not an indication to stop ATV. Psychological impact of jaundice should be evaluated, and alternative agents should be considered. Jaundice may result in nonadherence, particularly in adolescents; this side effect should be discussed with patients.
Non-Cirrhotic Portal Hypertension	d4T, ddI The Panel **no longer recommends** the use of these agents.	**Onset:** • Generally after years of therapy; may occur years after stopping therapy. **Presentation:** • GI bleeding, esophageal varices, and hypersplenism • Mild elevations in AST and ALT levels, moderate increases in ALP levels, and pancytopenia **Liver Biopsy Findings:** • The most commonly seen findings include nodular regenerative hyperplasia and hepatoportal sclerosis.	Rare	Prolonged exposure to ddI and the combination of d4T and ddI.	No specific monitoring	Manage complications of GI bleeding and esophageal varices.

[a] For example, HLA-DRB1*0101 in white people, HLA-DRB1*0102 in South Africans, and HLA-B35 in Thai people and white people.

[b] Less-frequent monitoring can be considered in children whose clinical status has been stable for >2 years to 3 years (see Clinical and Laboratory Monitoring of Pediatric HIV Infection).

Key: 3TC = lamivudine; ABC = abacavir; ALP = alkaline phosphatase; ALT = alanine transaminase; ARV = antiretroviral; AST = aspartate aminotransferase; ATV = atazanavir; CD4 = CD4 T lymphocyte; CMV = cytomegalovirus; d4T = stavudine; ddI = didanosine; DTG = dolutegravir; EBV = Epstein-Barr virus; EFV = efavirenz; FTC = emtricitabine; GI = gastrointestinal; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HLA = human leukocyte antigen; HSR = hypersensitivity reaction; IRIS = immune reconstitution inflammatory syndrome; MVC = maraviroc; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; the Panel = Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV; PI = protease inhibitor; RAL = raltegravir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ULN = upper limit of normal; ZDV = zidovudine

Table 15f. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Insulin Resistance, Asymptomatic Hyperglycemia, Diabetes Mellitus (Last updated April 14, 2020; last reviewed April 14, 2020)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Insulin Resistance, Asymptomatic Hyperglycemia, DM[a]	ZDV, LPV/r, and possibly other PIs	**Onset:** • Weeks to months after beginning therapy **Presentation:** • Asymptomatic fasting hyperglycemia (which sometimes occurs in the setting of lipodystrophy), metabolic syndrome, or growth delay • Symptomatic DM (rare)	**Children:** • Insulin resistance, 6% to 12% (incidence is higher during puberty, 20% to 30%) • Impaired fasting glucose, 0% to 7% • Impaired glucose tolerance, 3% to 4% • DM, 0.2 per 100 child-years	**Risk Factors for Type 2 DM:** • Lipodystrophy • Metabolic syndrome • Family history of DM • High BMI (obesity)	**Prevention:** • Lifestyle modification **Monitoring:** • Monitor for signs of DM, change in body habitus, and acanthosis nigricans. • Obtain RPG levels at initiation of ART, 3–6 months after ART initiation, and yearly thereafter. • In patients with an RPG ≥140 mg/dL, obtain FPG after an 8-hour fast and consider referring the patient to an endocrinologist.	Counsel patient on lifestyle modification (e.g., implementing a diet low in saturated fat, cholesterol, trans fat, and refined sugars; increasing physical activity; ceasing smoking). Recommend that the patient consult with a dietician. If the patient is receiving ZDV, switch to TAF, TDF, or ABC. **For Patients with Either an RPG ≥200 mg/dL Plus Symptoms of DM or an FPG ≥126 mg/dL:** • These patients meet diagnostic criteria for DM; consult an endocrinologist. **For Patients with an FPG of 100–125 mg/dL:** • Impaired FPG suggests insulin resistance; consult an endocrinologist. **For Patients with an FPG <100 mg/dL:** • This FPG is normal, but a normal FPG does not exclude insulin resistance. Recheck FPG in 6–12 months.

[a] Insulin resistance, asymptomatic hyperglycemia, and DM form a spectrum of increasing severity.

Insulin Resistance: Often defined as elevated insulin levels for the level of glucose observed.

Impaired FPG: Often defined as an FPG of 100–125 mg/dL.

Impaired Glucose Tolerance: Often defined as an elevated 2-hour PG of 140–199 mg/dL in a 75-g OGTT (or, if the patient weighs <43 kg, 1.75 g per kg of glucose up to a maximum of 75 g).

DM: Often defined as either an FPG ≥126 mg/dL, an RPG ≥200 mg/dL in a patient with hyperglycemia symptoms, an HgbA1c of ≥6.5%, or a 2-hour PG ≥200 mg/dL in an OGTT.

However, the Panel does not recommend performing routine measurements of insulin levels, HgbA1c, or glucose tolerance without consulting an endocrinologist. These guidelines are instead based on the readily available RPG and FPG levels.

Key: ABC = abacavir; ARV = antiretroviral; BMI = body mass index; dL = deciliter; DM = diabetes mellitus; FPG = fasting plasma glucose; HgbA1c = glycosylated hemoglobin; LPV/r = lopinavir/ritonavir; OGTT = oral glucose tolerance test; the Panel = Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV; PG = plasma glucose; PI = protease inhibitor; RPG = random plasma glucose; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

Table 15g. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Lactic Acidosis

(Last updated April 14, 2020; last reviewed April 14, 2020) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Lactic Acidosis	**NRTIs:** • ZDV • Less likely with 3TC, FTC, ABC, TAF, and TDF **Other Drugs:** • See the Risk Factors and Prevention/ Monitoring columns for information regarding the toxicity of propylene glycol when LPV/r oral solution is used in neonates.	**Onset:** • Generally after years of exposure **Presentation:** • Lactic acidosis may be clinically asymptomatic. *Lactic Acidosis May Also Present with Insidious Onset of a Combination of Signs and Symptoms:* • Generalized fatigue, weakness, and myalgias • Vague abdominal pain, weight loss, unexplained nausea, or vomiting • Dyspnea • Peripheral neuropathy **Note:** Patients may present with acute multi-organ failure (e.g., fulminant hepatic failure, pancreatic failure, respiratory failure).	Lactic acidosis is associated with use of ddI and d4T. Cases are rare now that these NRTIs **are no longer recommended**. 3TC, FTC, ABC, TAF, and TDF are less likely to induce clinically significant mitochondrial dysfunction than ZDV.	**Adults:** • Female sex • High BMI • Chronic HCV infection • African-American race • Coadministration of TDF with metformin • Overdose of propylene glycol • CD4 count <350 cells/ mm^3 • Acquired riboflavin or thiamine deficiency • Possibly pregnancy **Preterm Infants or Any Neonates Who Have Not Attained a Post-Menstrual Age of 42 Weeks and a Postnatal Age of ≥14 Days:** • Exposure to propylene glycol, which is used as a diluent in LPV/r oral solution. A diminished ability to metabolize propylene glycol may lead to accumulation, increasing the risk of adverse events.	**Prevention:** • Due to the presence of propylene glycol as a diluent, LPV/r oral solution **should not be used** in preterm neonates or any neonate who has not attained a postmenstrual age of 42 weeks and a postnatal age of ≥14 days. • Monitor for clinical manifestations of lactic acidosis and promptly adjust therapy. **Monitoring** *Asymptomatic Patients:* • Measurement of serum lactate **is not recommended**. *Patients with Clinical Signs or Symptoms Consistent with Lactic Acidosis:* • Obtain blood lactate level.[a] • Additional diagnostic evaluations should include serum bicarbonate, anion gap, and/or arterial blood gas; amylase and lipase; serum albumin; and hepatic transaminases.	**For Patients with Lactate 2.1–5.0 mmol/L (Confirmed with a Second Test):** • Consider discontinuing all ARV drugs temporarily while conducting additional diagnostic workup. **For Patients with Lactate >5.0 mmol/L (Confirmed With a Second Test)[b] or >10.0 mmol/L (Any One Test):** • Discontinue all ARV drugs. • Provide supportive therapy (e.g., IV fluids; some patients may require sedation and respiratory support to reduce oxygen demand and ensure adequate oxygenation of tissues). **Anecdotal (Unproven) Supportive Therapies:** • Administer bicarbonate infusions, THAM, high doses of thiamine and riboflavin, oral antioxidants (e.g., L-carnitine, co-enzyme Q10, vitamin C) Following the resolution of clinical and laboratory abnormalities, resume therapy, either with an NRTI-sparing regimen or a revised NRTI-containing regimen. Institute a revised NRTI-containing regimen with caution, using NRTIs that are less likely to induce mitochondrial dysfunction (ABC, TAF, TDF, FTC or 3TC). Lactate should be monitored monthly for ≥3 months.

Table 15g. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Lactic Acidosis

(Last updated April 14, 2020; last reviewed April 14, 2020) (page 2 of 2)

[a] Blood for lactate determination should be collected, without prolonged tourniquet application or fist clenching, into a pre-chilled, gray-top, fluoride-oxalate-containing tube and transported on ice to the laboratory to be processed within 4 hours of collection.

[b] Management can be initiated before receiving the results of the confirmatory test.

Key: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; BMI = body mass index; CD4 = CD4 T lymphocyte; d4T = stavudine; ddI = didanosine; FTC = emtricitabine; HCV = hepatitis C virus; IV = intravenous; LPV/r = lopinavir/ritonavir; NRTI = nucleoside reverse transcriptase inhibitor; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; THAM = tris (hydroxymethyl) aminomethane; ZDV = zidovudine

Table 15h. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Lipodystrophies and Weight Gain (Last updated April 14, 2020; last reviewed April 14, 2020) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Lipodystrophy (Fat Maldistribution) General Information	See below for specific associations.	**Onset:** • Increase in trunk and limb fat are the first sign; peripheral fat wasting may not appear for 12–24 months after ART initiation.	Frequency is low (<5%) with current regimens.	Genetic predisposition Puberty HIV-associated inflammation Older age Longer duration of ART Body habitus	**Prevention:** • Initiate a calorically appropriate, low-fat diet and an exercise regimen. **Monitoring:** • BMI measurement • Waist circumference and waist-hip ratio	Physicians should perform a regimen review and consider changing the regimen when lipodystrophy occurs. Improvement in fat maldistribution can vary following a regimen change. Improvement may occur after several months or years, or it may not occur at all.
Central Lipohypertrophy or **Lipo-accumulation**	Can occur in the absence of ART, but these conditions are most often associated with the use of PIs and EFV.	**Presentation:** • Central fat accumulation with increased abdominal girth, which may include a dorsocervical fat pad (buffalo hump). Gynecomastia may occur in males or breast hypertrophy may occur in females, particularly with the use of EFV.	Frequency is low (<5%) with current regimens.	Obesity before initiation of therapy Sedentary lifestyle	**Prevention:** • Initiate a calorically appropriate, low-fat diet and an exercise regimen. **Monitoring:** • BMI measurement • Waist circumference and waist-hip ratio	Counsel patient on lifestyle modification and dietary interventions (e.g., maintaining a calorically appropriate diet that is low in saturated fats and simple carbohydrates, and starting an exercise regimen, especially strength training). Recommend smoking cessation (if applicable) to decrease future CVD risk. Consider using an INSTI instead of a PI or EFV, although some INSTIs may be associated with generalized weight gain (see below). **Data are Insufficient to Allow the Panel to Safely Recommend Use of Any of the Following Modalities in Children:** • Recombinant human growth hormone • Growth hormone-releasing hormone • Metformin • Thiazolidinediones • Recombinant human leptin • Anabolic steroids • Liposuction

Table 15h. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Lipodystrophies and Weight Gain (Last updated April 14, 2020; last reviewed April 14, 2020) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Facial/Peripheral Lipoatrophy	Most cases are associated with the use of ZDV, a thymidine analogue NRTI.	**Presentation:** • Thinning of subcutaneous fat in the face, buttocks, and extremities, measured as a decrease in trunk/limb fat by DXA or triceps skinfold thickness. Preservation of lean body mass distinguishes lipoatrophy from HIV-associated wasting.	Frequency is low (<5%) with current regimens.	Underweight before ART initiation	**Prevention:** • Limit the use of ZDV. **Monitoring:** • Patient self-report and physical examination are the most sensitive methods of monitoring lipoatrophy.	Replace ZDV with another NRTI when possible. **Data are Insufficient to Allow the Panel to Safely Recommend Use of Any of the Following Modalities in Children:** • Injections of poly-L-lactic acid • Recombinant human leptin • Autologous fat transplantation • Thiazolidinediones
Weight Gain	Significant weight gain may occur with all ARV regimens, but it appears to be more pronounced with DTG, BIC, and TAF.	Gradual weight gain after initiating ARV drugs is common with all currently used regimens. The mechanism for weight gain is unclear and is under investigation.	Rate of development of obesity is unclear.	**In Adults:** • Low pre-treatment BMI • Older age • Female sex • Black race Risk factors for weight gain have not yet been evaluated in infants and children.	**Prevention:** • Initiate a calorically appropriate, low-fat diet and an exercise regimen. **Monitoring:** • BMI measurement • Waist circumference and waist-hip ratio	Counsel patient on lifestyle modification and dietary interventions (e.g., maintaining a calorically appropriate, healthy diet that is low in saturated fats and simple carbohydrates, and starting an exercise regimen, especially strength training).

Key: ART = antiretroviral therapy; ARV = antiretroviral; BIC = bictegravir; BMI = body mass index; CVD = cardiovascular disease; DTG = dolutegravir; DXA = dual energy x-ray absorptiometry; EFV = efavirenz; INSTI = integrase strand transfer inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; TAF = tenofovir alafenamide; ZDV = zidovudine

Table 15i. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Nephrotoxic Effects

(Last updated April 14, 2020; last reviewed April 14, 2020) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Urolithiasis/ Nephrolithiasis	ATV DRV causes crystalluria, but it is not associated with nephrolithiasis.	**Onset:** • Weeks to months after starting therapy **Clinical Findings:** • Crystalluria • Hematuria • Pyuria • Flank pain • Increased creatinine levels in some cases	ATV-related nephrolithiasis occurs in <10% of patients and has been reported after stopping ATV.	In adults, elevated urine pH (>5.7) The risk factors in children are unknown.	**Prevention:** • Maintain adequate hydration. **Monitoring:** • Obtain urinalysis at least every 6–12 months.	Provide adequate hydration and pain control. Consider using another ARV drug in place of ATV.
Renal Dysfunction	TDF	**Onset:** • Variable; in adults, renal dysfunction may occur weeks to months after initiating therapy. • Hypophosphatemia appears at a median of 18 months. • Glucosuria may occur after 1 year of therapy. • Abnormal urine protein/osmolality ratio may be an early indicator. **Presentation** *More Common:* • Increased serum creatinine levels, proteinuria, normoglycemic glucosuria • Increased urinary protein/creatinine ratio and albumin/creatinine ratio • Hypophosphatemia, usually asymptomatic; may present with bone and muscle pain or muscle weakness *Less Common:* • Renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis, nephrogenic diabetes insipidus with polyuria	**Adults:** • Approximately 2% of adults experience increased serum creatinine levels. • Approximately 0.5% of adults experience severe renal complications. **Children:** • Approximately 4% of children experience hypophosphatemia or proximal tubulopathy; frequency increases with prolonged TDF therapy and advanced HIV infection.	**Risk May Increase in Children with the Following Characteristics:** • Aged >6 years • Black race, Hispanic/ Latino ethnicity • Advanced HIV infection • Hypertension • Diabetes • Concurrent use of PIs (especially LPV/r) and preexisting renal dysfunction • Longer duration of TDF treatment • The presence of the apolipoprotein L1 variants G1 and G2 appears to increase the risk of renal abnormality in children with HIV. These alleles are more common in persons of black descent.	Monitor urine protein, urine glucose and serum creatinine at 3-month to 6-month intervals. Some Panel members routinely monitor serum phosphate levels in patients who are taking TDF. Measure serum phosphate if the patient experiences persistent proteinuria or glucosuria, or has symptoms of bone pain, muscle pain, or weakness. Because toxicity risk increases with the duration of TDF treatment, do not decrease the frequency of monitoring over time.	If TDF is the likely cause, consider using an alternative ARV drug. TAF has significantly less toxicity than TDF.

Table 15i. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Nephrotoxic Effects

(Last updated April 14, 2020; last reviewed April 14, 2020) **(page 2 of 2)**

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Elevation in Serum Creatinine	DTG, COBI, RPV, BIC	**Onset:** • Within a month of starting treatment **Presentation:** • Asymptomatic. These drugs decrease renal tubular secretion of creatinine, leading to an increase in serum creatinine levels without a true change in eGFR.	Common Clinicians need to distinguish between a true change in eGFR and other causes. A true change may be associated with other medical conditions, the continuing rise of serum creatinine levels over time, and albuminuria.	The risk factors in children are unknown.	Monitor serum creatinine. Assess for renal dysfunction if serum creatinine increases by >0.4 mg/dL or if increases continue over time.	No need to change therapy. Reassure the patient about the benign nature of the laboratory abnormality.

Key: ARV = antiretroviral; ATV = atazanavir; BIC = bictegravir; COBI = cobicistat; dL = deciliter; DRV = darunavir; DTG = dolutegravir; eGFR = estimated glomerular filtration rate; LPV/r = lopinavir/ritonavir; PI = protease inhibitor; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Table 15j. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Osteopenia and Osteoporosis (Last updated April 14, 2020; last reviewed April 14, 2020)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Osteopenia and **Osteoporosis**	Any ART regimen **Specific Agents of Concern:** • TDF, especially when used in a regimen that includes a boosting agent (i.e., RTV, COBI) • PIs	**Onset:** • Any age; decrease in BMD is usually seen soon after initiating ART. **Presentation:** • Usually asymptomatic • Rarely presents as osteoporosis, a clinical diagnosis defined by evidence of bone fragility (e.g., a fracture with minimal trauma).	**BMD z-Score Less Than -2.0:** • <10% in U.S. cohorts • Approximately 20% to 30% in international cohorts	Longer duration and greater severity of HIV disease Vitamin D insufficiency/ deficiency Delayed growth or pubertal delay Low BMI Lipodystrophy Non-black race Smoking Prolonged systemic corticosteroid use Medroxyprogesterone use Lack of weight-bearing exercise	**Prevention:** • Ensure that the patient has sufficient intake and levels of both calcium and vitamin D. • Encourage weight-bearing exercise. • Minimize modifiable risk factors (e.g., smoking, low BMI, use of steroids or medroxyprogesterone). • Use TAF instead of TDF whenever possible. • Use TDF with EFV or an unboosted INSTI. • When using TDF in a regimen, consider supplementing with vitamin D3 at a daily dose of 1,000–4,000 IU. **Monitoring:** • Assess nutritional intake (calcium, vitamin D, and total **c**alories). • Strongly consider measuring serum 25-OH-vitamin D levels, particulary in patients who are taking ARV drugs of concern.[a] • DXA is rarely indicated.[b]	Same options as for prevention. Consider changing the ARV regimen (e.g., switching from TDF to TAF, and/or from LPV/r to EFV or an unboosted INSTI whenever possible). Treat patient with vitamin D3 to raise serum 25-OH-vitamin D concentrations to >30 ng/mL. There is no clear benefit to administering daily supplemental vitamin D3 doses that are >4,000 IU. If patients are receiving a daily dose of vitamin D3 that is >4,000 IU, consider monitoring levels of 25-OH-vitamin D. An increase in BMD was seen in one study that evaluated the use of alendronate in youth with HIV. However, the role of bisphosphonates in managing osteopenia and osteoporosis in children with HIV has not been established.

[a] Some experts periodically measure 25-OH-vitamin D. This is especially important in children and adolescents with HIV who live in urban areas; the prevalence of vitamin D insufficiency is high in that population.

[b] Until more data are available on the long-term effects of TDF on bone mineral acquisition in childhood, DXA scanning is not usually recommended for children who are being treated with TDF. DXA scanning could be considered for youth who are receiving TDF along with additional medications which affect bone density and for children with indications that are not uniquely related to HIV infection (such as cerebral palsy).

Key: ART = antiretroviral therapy; ARV = antiretroviral; BMD = bone mineral density; BMI = body mass index; COBI = cobicistat; DXA = dual-energy x-ray absorptiometry; EFV = efavirenz; INSTI = integrase strand transfer inhibitor; IU = international unit; LPV/r = lopinavir/ritonavir; ng = nanogram; PI = protease inhibitor; RTV = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Table 15k. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions (Last updated April 14, 2020; last reviewed April 14, 2020) (1 of 4)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Rash	Any ARV drug can cause rash.	**Onset:** • First few days to weeks after starting new ARV drug(s) **Presentation:** • Most rashes are mild-to-moderate, diffuse maculopapular eruptions. **Note:** A rash can be the initial manifestation of systemic hypersensitivity (see the SJS/TEN/EM major and HSR sections below).	**Common (>10%):** • EFV • ETR • FTC • NVP **Less Common (5% to 10%):** • ABC • ATV • DRV • TDF **Unusual (2% to 4%):** • LPV/r • MVC • RAL • RPV	Sulfonamide allergy is a risk factor for rash in patients who are taking PIs that contain a sulfonamide moiety (i.e., DRV). Polymorphisms in CYP2B6 and multiple HLA loci are associated with an increased risk of rash in patients who are taking NVP.	**When Starting NVP or Restarting NVP After Interruptions of >14 Days:** • Utilize once-daily lead-in dosing.[a] This may not be necessary in children aged <2 years.[b] • Avoid the use of systemic corticosteroids during NVP dose escalation. • Assess patient for rash severity, mucosal involvement, and other signs of systemic reaction.	**Mild-to-Moderate Maculopapular Rash Without Systemic or Mucosal Involvement:** • Most rashes will resolve without intervention; ARV drugs can be continued while monitoring.[a] • Antihistamines may provide some relief. **Severe Rash and/or Rash Accompanied by Systemic Symptoms:** • Manage as SJS/TEN/EM major, DRESS, or HSR as applicable (see below). **Rash in Patients Receiving NVP:** • Given the elevated risk of HSR, measure hepatic transaminases. • If hepatic transaminases are elevated, NVP **should be discontinued and not restarted** (see the HSR section below).
SJS/TEN/ EM Major	Many ARV drugs, especially NNRTIs (see the Estimated Frequency column)	**Onset:** • First few days to weeks after starting new ARV drug(s) **Presentation:** • Initial rash may be mild, but it often becomes painful, evolving to blister/bulla formation with necrosis in severe cases. Usually involves mucous membrane ulceration and/or conjunctivitis. Systemic symptoms may also include fever, tachycardia, malaise, myalgia, and arthralgia.	**Infrequent:** • NVP (0.3%) • EFV (0.1%) • ETR (<0.1%) **Case Reports:** • ABC • ATV • DRV • LPV/r • RAL • ZDV	**Adults:** • Female sex • Patients who are black, Asian, or Hispanic are at higher risk.	**When Starting NVP or Restarting NVP After Interruptions of >14 Days:** • Utilize once-daily lead-in dosing.[a] This may not be necessary in children aged <2 years.[b] • Counsel families to report symptoms as soon as they appear.	Discontinue all ARV drugs and other possible causative agents (e.g., TMP-SMX). Provide intensive supportive care, including IV hydration, aggressive wound care, eye care, labial adhesion preventative care, pain management, and antipyretics. Parenteral nutrition and antibiotics may also be necessary. Corticosteroids and/or IVIG are sometimes used, but the use of these interventions is controversial. **Do not reintroduce** the offending medication. In cases where a patient experiences SJS/TEN/EM major while taking an NNRTI, many experts would avoid using other NNRTIs when restarting ART.

Table 15k. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions (Last updated April 14, 2020; last reviewed April 14, 2020) (2 of 4)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
DRESS	DRV, DTG, EFV, ETR, NVP, RAL, RPV	**Onset:** • 1–8 weeks after starting new ARV drug(s) **Presentation:** • Fever • Lymphadenopathy • Facial swelling • Morbilliform to polymorphous rash • Peripheral eosinophilia • Atypical circulating lymphocytes • Internal organ involvement (particularly the liver and/or kidneys)	Rare	Unknown	Obtain a CBC and AST, ALT, and creatinine levels from patients who present with suggestive symptoms.	Discontinue all ARV drugs and other possible causative agents (e.g., TMP-SMX). The role of systemic steroids in treatment is unclear; consultation with a specialist is recommended. Provide supportive care for endorgan disease. **Do not reintroduce** the offending medication.
HSR With or without skin involvement and excluding SJS/TEN	ABC	**Onset** *With First Use:* • Within first 6 weeks of initiating ABC *With Reintroduction:* • Within hours of initiating ABC **Presentation:** • Symptoms include high fever, diffuse skin rash, malaise, nausea, headache, myalgia, arthralgia, diarrhea, vomiting, abdominal pain, pharyngitis, and respiratory symptoms (e.g., dyspnea). • With continuation of ABC, symptoms may progress to hypotension and vascular collapse. With rechallenge, symptoms can mimic anaphylaxis.	<1% to 9% (varies by ethnicity)	HLAB*5701 (HSR is very uncommon in people who are HLAB*5701 negative). The risk of HSR is higher in patients who are white than in patients who are black or East Asian.	Screen for HLAB*5701. **ABC should not be prescribed if HLAB*5701 is present**. The medical record should clearly indicate that ABC is **contraindicated** in these patients. When starting ABC, counsel patients and families about the signs and symptoms of HSR to ensure prompt reporting of reactions.	Discontinue all ARV drugs and investigate other causes of the symptoms (e.g., a concurrent viral illness). Provide symptomatic treatment. Most symptoms resolve within 48 hours after discontinuing ABC. **Do not rechallenge** with ABC even if the patient is HLAB*5701 negative.

Table 15k. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions (Last updated April 14, 2020; last reviewed April 14, 2020) (3 of 4)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
HSR, continued	NVP	**Onset:** • Occurs most frequently in the first few weeks of therapy, but can occur through 18 weeks **Presentation:** • Flulike symptoms (including nausea, vomiting, myalgia, fatigue, fever, abdominal pain, and jaundice) with or without skin rash that may progress to hepatic failure with encephalopathy	Occurs in 4% of patients on average, with a range of 2.5% to 11%	**Adults:** • ARV-naive with a higher CD4 count (>250 cells/mm^3 in women; >400 cells/mm^3 in men) • Female sex (risk is 3-fold higher in females than in males). **Children:** • NVP hepatotoxicity and HSR are less common in prepubertal children than in adults, and both are uncommon in infants. • High CD4 percentage is associated with an increased risk of NVP toxicity. In the PREDICT study, the risk of NVP toxicity (rash, hepatotoxicity, and hypersensitivity) was 2.65 times greater in children who had CD4 percentages ≥15% than in children who had CD4 percentages <15%.	**When Starting NVP or Restarting NVP After Interruptions of >14 Days:** • A 2-week lead-in period with once-daily dosing, followed by dose escalation to twice daily as recommended, may reduce the risk of reaction.[a] This may not be necessary in children aged <2 years.[b] • Counsel families about signs and symptoms of HSR to ensure prompt reporting of reactions. • Obtain AST and ALT levels in patients with rash. • Obtain AST and ALT levels at baseline, before dose escalation, 2 weeks after dose escalation, and thereafter at 3-month intervals. • Avoid NVP use in women with CD4 counts >250 cells/mm^3 and in men with CD4 counts >400 cells/mm^3, unless benefits outweigh risks. • Do not use NVP as PEP outside of the neonatal period.	Discontinue all ARV drugs. Consider other causes for hepatitis and discontinue all hepatotoxic medications. Provide supportive care as indicated and monitor the patient closely. **Do not reintroduce NVP.** It is unclear whether it is safe to use other NNRTIs after a patient experiences symptomatic hepatitis due to NVP, and many experts would avoid the NNRTI drug class when restarting treatment.

Table 15k. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions (Last updated April 14, 2020; last reviewed April 14, 2020) (4 of 4)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
HSR, continued	ETR	**Onset:** • Any time during therapy **Presentation:** • Symptoms may include rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure.	Rare	Unknown	Evaluate for hypersensitivity if the patient is symptomatic.	Discontinue all ARV drugs. Rechallenge with ETR **is not recommended**.
	MVC	Rash preceding hepatotoxicity	Rare	Unknown	Obtain AST and ALT levels from patients with rash or other symptoms of hypersensitivity.	Discontinue all ARV drugs. Rechallenge with MVC **is not recommended**.
	DTG	Rash with hepatic dysfunction	Rare	Unknown	Obtain AST and ALT levels from patients with rash or other symptoms of hypersensitivity.	Discontinue all ARV drugs. Rechallenge with DTG is **contraindicated**.

[a] The prescribing information for NVP states that patients who experience rash during the 14-day lead-in period should not have the NVP dose increased until the rash has resolved. However, prolonging the lead-in phase beyond 14 days may increase the risk of NVP resistance because of subtherapeutic drug levels. Children who have persistent mild or moderate rash after the lead-in period should receive individualized care. Consult an expert in HIV care when managing these patients. **NVP should be stopped and not restarted** if the rash is severe or progressing. See the Nevirapine section of the Drug Appendix.

[b] Lead-in dosing **is not recommended** when using NVP for either presumptive or definitive HIV therapy in newborns with perinatal HIV exposure or perinatal HIV infection. See the Nevirapine section of the Drug Appendix and Table 12.

Key: ABC = abacavir; ALT = alanine transaminase; ART = antiretroviral therapy; ARV = antiretroviral; AST = aspartate aminotransferase; ATV = atazanavir; CBC = complete blood count; CD4 = CD4 T lymphocyte; CYP = cytochrome P; DRESS = drug reaction (or rash) with eosinophilia and systemic symptoms; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EM = erythema multiforme; ETR = etravirine; FTC = emtricitabine; HLA = human leukocyte antigen; HSR = hypersensitivity reaction; IV = intravenous; IVIG = intravenous immune globulin; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PEP = post-exposure prophylaxis; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; SJS = Stevens-Johnson syndrome; TDF = tenofovir disoproxil fumarate; TEN = toxic epidermal necrolysis; TMP-SMX = trimethoprim-sulfamethoxazole; ZDV = zidovudine

Table 16. Examples of Changes in Antiretroviral Regimen Components for Children with Sustained Virologic Suppression (page 1 of 3)

This list is not exhaustive and does not necessarily contain all potential treatment options. Instead, it provides examples of changes that could be made. The table only includes information about switching between ARV drugs; **it does not include all the information that clinicians should consider before prescribing these drugs, such as drug cost and the patient's insurance coverage**. Please refer to individual drug sections, Table 1, and Table 2 in Appendix A: Pediatric Antiretroviral Drug Information for further information about the use of specific ARV drugs and FDC formulations.

Current ARV Drug(s)	Age, Weight, and SMR Requirements	Potential ARV Drug Switch	Comment
NRTIs			
ABC Twice Daily	Aged ≥1 year	ABC once daily	See the Abacavir[a] section.
3TC Twice Daily	Aged ≥3 years	3TC once daily	See the Lamivudine section.
	Any age (starting at full-term birth) Any weight	FTC once daily	See the Emtricitabine section.
ZDV, ddI, or d4T[b] **Note:** ddI and d4T should be replaced as soon as possible due to concerns about toxicity.	Aged ≥3 months	ABC	Less long-term mitochondrial toxicity. Children aged ≥1 year can take ABC once daily.
	Aged ≥2 years Weighing 17 kg to <25 kg	TDF	TDF is a reasonable, once-daily option for HLA-B*5701-positive children for whom ABC is not recommended. TDF is available as an oral powder and low-strength tablets alone or in combination with FTC.
	Aged ≥2 years Weighing ≥25 kg	TAF[c]	Less long-term mitochondrial toxicity. Once-daily dosing. Coformulation with other ARV drugs can further reduce pill burden. TAF is preferred over TDF because of the lower risk of bone and renal toxicity.
NNRTIs			
NVP or EFV	Any age (starting at full-term birth) Weighing ≥2 kg	RAL[d]	RAL has a potentially greater barrier to resistance than NVP. Both are dosed twice daily in children.
	Aged ≥3 months Weighing ≥5 kg	ATV/r	ATV/r has a potentially greater barrier to resistance; however, taking ATV/r may be difficult for some patients, as ATV oral powder must be mixed with food or a beverage before administration, and the palatability of the RTV oral solution is poor.
	Aged ≥3 years Weighing ≥10 kg	DRV/r	DRV/r has a potentially greater barrier to resistance. DRV/r is administered twice daily to patients aged <12 years, but may be administered once daily in children aged ≥12 years who do not have any DRV resistance mutations.

Table 16. Examples of Changes in Antiretroviral Regimen Components for Children with Sustained Virologic Suppression (page 2 of 3)

Current ARV Drug(s)	Age, Weight, and SMR Requirements	Potential ARV Drug Switch	Comment
NNRTIs, continued			
NVP or EFV, continued	Weighing ≥25 kg	BIC as Biktarvy	Once-daily dosing. BIC is available as a component of the FDC tablet BIC/FTC/TAF (Biktarvy), which is a complete ARV regimen that can be taken with or without food.
	Weighing ≥25 kg	EVG as Genvoya	EVG is available as a component of the FDC tablet EVG/c/FTC/TAF (Genvoya), which is a complete ARV regimen that must be taken with food.
	Weighing ≥20 kg	DTG	DTG is available as a smaller, single-drug tablet or as an FDC tablet, both of which can be dosed once daily if no INSTI resistance mutations have been previously detected. DTG plus the weight-appropriate dose of FTC/TDF (Truvada) can be used in children weighing 20 kg to <25 kg. DTG is available as a component of the FDC tablet ABC/DTG/3TC (Triumeq), which is a complete ARV regimen that can be given to children weighing ≥25 kg. Higher barrier to resistance, which makes it a good choice for patients who have poor adherence. May improve lipid levels. See the Dolutegravir section for information regarding use of DTG in female adolescents of childbearing potential and pregnant adolescents.[e]
	Aged ≥12 years Weighing ≥35 kg	RPV	Lower incidence of adverse lipid effects.
PIs			
LPV/r Twice Daily	Any age (starting at full-term birth) Weighing ≥2 kg	RAL[d]	Better palatability. RAL HD can only be given once daily in those weighing ≥40 kg. Unlike LPV/r, the use of RAL is not restricted to infants with a corrected gestational age of ≥42 weeks and a postnatal age of ≥14 days. RAL granules may be difficult to dose for some caregivers.
	Aged ≥3 years Weighing ≥10 kg	EFV	Once-daily dosing. Better palatability. Lower incidence of adverse lipid effects. See the Efavirenz section for concerns about EFV dosing for children aged <3 years.
	Aged ≥3 months Weighing ≥5 kg	ATV/r	Once-daily dosing. ATV/r may have a lower incidence of adverse lipid effects; however, taking ATV/r may be difficult for some patients, as ATV oral powder must be mixed with food or a beverage before administration, and the palatability of the RTV oral solution is poor.
	Aged ≥3 years Weighing ≥10 kg	DRV/r	DRV/r may have a lower incidence of adverse lipid effects. DRV/r is administered twice daily to patients aged <12 years, but may be administered once daily in children aged ≥12 years who do not have DRV resistance mutations.
	Weighing ≥25 kg	EVG as Genvoya	EVG is available as a component of the FDC tablet EVG/c/FTC/TAF (Genvoya), which is a complete ARV regimen that must be taken with food.
	Weighing ≥20 kg	DTG	Once-daily dosing if no INSTI resistance mutations have been previously detected. May be better tolerated, and can be given as an FDC tablet to children weighing ≥25 kg. DTG plus the weight-appropriate dose of FTC/TDF (Truvada) can be used in children weighing 20 kg to <25 kg. May improve lipid levels. See the Dolutegravir section for information regarding use of DTG in female adolescents of childbearing potential and pregnant adolescents.[e]
	Aged ≥12 years Weighing ≥35 kg	RPV	May be better tolerated. Lower incidence of adverse lipid effects.
	Weighing ≥25 kg	BIC as Biktarvy	Once-daily dosing. BIC is available as a component of the FDC tablet BIC/FTC/TAF (Biktarvy), which is a complete ARV regimen that can be taken with or without food.
Other			
Any Multi-Pill and/or Twice-Daily Regimen	Weighing ≥25 kg	EVG/c/FTC/TAF (Genvoya)	Once-daily dosing. Single pill. Alignment with adult regimens. Must be taken with food.
	Weighing ≥25 kg	FTC/TAF[c] (Descovy) plus DTG	Once-daily dosing. This regimen may be more desirable because of smaller pill sizes, but it has a higher pill burden (two pills instead of one). Aligns a child's regimen with an efficacious regimen that is used in adults. See the Dolutegravir section for information regarding use of DTG in female adolescents of childbearing potential and pregnant adolescents.[e]

Table 16. Examples of Changes in Antiretroviral Regimen Components for Children with Sustained Virologic Suppression (page 3 of 3)

Current ARV Drug(s)	Age, Weight, and SMR Requirements	Potential ARV Drug Switch	Comment
Other, continued			
Any Multi-Pill and/or Twice-Daily Regimen, continued	Weighing ≥35 kg SMR 4 or 5	EVG/c/FTC/TDF (Stribild)	Once-daily dosing. Single pill. Aligns a child's regimen with an efficacious regimen that is used in adults. Must be taken with food. Renal and bone toxicity of TDF limit its use.
	Aged ≥12 years Weighing ≥35 kg	FTC/RPV/TAF (Odefsey)	Once-daily dosing. Single pill. Aligns a child's regimen with an efficacious regimen that is used in adults. Must be taken with food at a consistent time daily.
	Weighing ≥25 kg	BIC/FTC/TAF (Biktarvy)	Once-daily dosing. Single pill that can be taken with or without food.
	Aged ≥12 years Weighing ≥35 kg SMR 4 or 5	FTC/RPV/TDF (Complera)	Once-daily dosing. Single pill. Aligns a child's regimen with an efficacious regimen that is used in adults. Must be taken with food at consistent time daily. Renal and bone toxicity of TDF limit its use.
	Weighing ≥25 kg	ABC/DTG/3TC (Triumeq)	Once-daily dosing. Single pill. Aligns a child's regimen with an efficacious regimen that is used in adults. Large pill size may be a deterrent. See the Dolutegravir section for information regarding use of DTG in female adolescents of childbearing potential and pregnant adolescents.[e]
	Weighing ≥40 kg SMR 4 or 5	EFV/FTC/TDF (Atripla)	Once-daily dosing. Single pill. Aligns a child's regimen with an efficacious regimen that is used in adults. Renal and bone toxicity of TDF as well as CNS toxicity of EFV limit its use.

[a] For infants and young children who are being treated with liquid formulations of ABC, initiation with once-daily ABC is not generally recommended. In clinically stable patients with undetectable viral loads who have had stable CD4 counts for >6 months (24 weeks) on twice-daily ABC, the dose can be changed from twice daily to once daily.

[b] See Archived Drugs in Appendix A: Pediatric Antiretroviral Drug Information.

[c] For children and adolescents weighing 25 kg to <35 kg, TAF can be used in combination with an INSTI or an NNRTI, but **not** a boosted PI. For children and adolescents weighing ≥35 kg, TAF can be used in combination with an INSTI, NNRTI, or a boosted PI.

[d] RAL is recommended for twice-daily use in children. Chewable tablets can be used as dispersible tablets starting at 4 weeks of age. RAL HD once daily is **only** recommended for virologically suppressed children weighing ≥40 kg.

[e] Exposure to DTG around the time of conception has been associated with a small but significant increase in the risk of infant neural tube defects. Additional information and specific recommendations about the use of DTG in adolescents and adults who are pregnant and those who are trying to conceive or who may become pregnant are available in the Adult and Adolescent Antiretroviral Guidelines (see Table 6b and Adolescents and Young Adults with HIV) and in the Perinatal Guidelines (see Teratogenicity, Recommendations for Use of Antiretroviral Drugs During Pregnancy, and Appendix D. Dolutegravir Counseling Guide for Health Care Providers).

Key: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; ATV/r = atazanavir/ritonavir; BIC = bictegravir; CD4 = CD4 T lymphocyte cell; CNS = central nervous system; d4T = stavudine; ddI = didanosine; DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDC = fixed-dose combination; FTC = emtricitabine; HD = high dose; HLA = human leukocyte antigen; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SMR = sexual maturity rating; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

Table 17. Discordance Among Virologic, Immunologic, and Clinical Responses

Differential Diagnosis of Poor Immunologic Response Despite Virologic Suppression
Poor Immunologic Response Despite Virologic Suppression and Good Clinical Response:
• Lab error (in CD4 value or viral load measurement)
• Misinterpretation of normal, age-related CD4 count decline (i.e., the immunologic response is not actually poor)
• Low pretreatment CD4 count or percentage
• AEs that are associated with the use of certain drugs (e.g., ZDV, TMP-SMX, systemic corticosteroids)
• Use of systemic corticosteroids or chemotherapeutic agents
• Conditions that can cause low CD4 values (e.g., HCV, acute viral infections, TB, malnutrition, Sjogren's syndrome, sarcoidosis, syphilis)
Poor Immunologic and Clinical Responses Despite Virologic Suppression:
• Lab error
• Falsely low viral load result for an HIV strain/type that is not detected by viral load assay (i.e., HIV-1 non-M groups, HIV-1 non-B subtypes, HIV-2)
• Persistent immunodeficiency that occurs soon after initiating ART but before ART-related reconstitution
• Primary protein-calorie malnutrition
• Untreated TB
• Malignancy
Differential Diagnosis of Poor Clinical Response Despite Adequate Virologic and Immunologic Responses
• IRIS
• A previously unrecognized, pre-existing infection or condition (e.g., TB, malignancy)
• Malnutrition
• Clinical manifestations of previous organ damage: brain (e.g., strokes, vasculopathy, worsening neurodevelopmental delay), lungs (e.g., bronchiectasis), cardiac (i.e., cardiomyopathy), renal (i.e., HIV-related kidney disease)
• A new clinical event due to a non-HIV illness or condition
• A new, otherwise unexplained HIV-related clinical event (e.g., treatment failure)

Key: AE = adverse effects; ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; HCV = hepatitis C virus; IRIS = immune reconstitution inflammatory syndrome; TB = tuberculosis; TMP-SMX = trimethoprim-sulfamethoxazole; ZDV = zidovudine

Table 18. Options for Regimens with at Least Two Fully Active Agents to Achieve Virologic Suppression in Patients with Virologic Failure and Evidence of Viral Resistance

Clinicians should evaluate a patient's treatment history and drug-resistance test results when choosing an ART regimen in order to optimize ARV drug effectiveness. This is particularly important when selecting the NRTI components of an NNRTI-based regimen, where drug resistance to the NNRTI can occur rapidly if the virus is not sufficiently sensitive to the NRTIs. Regimens should contain at least two, but preferably three, fully active drugs for durable and potent virologic suppression. If the M184V/I mutation associated with FTC and 3TC is present, these medications should be continued if the new regimen contains TDF, TAF, or ZDV. The presence of this mutation may increase susceptibility to these NRTIs.

Please see individual drug profiles for information about age limitations (e.g., do not use DRV in children aged <3 years), drug interactions, and dose adjustments when devising a regimen for children with multiclass drug resistance. Collaboration with a pediatric HIV specialist is especially important when choosing regimens for children with multiclass drug resistance. Regimens in this table are provided as examples, but the list is not exhaustive.

Prior Regimen	New Regimen Options[a]
Two NRTIs plus an NNRTI	Two NRTIs plus a boosted PI Two NRTIs plus an INSTI[b]
Two NRTIs plus a PI	Two NRTIs plus an INSTI Two NRTIs plus a different boosted PI INSTI plus a different boosted PI with or without an NNRTI and with or without NRTI(s)
Two NRTIs plus an INSTI	Two NRTIs plus a boosted PI DTG[a,b] or BIC[b] (if not used in the prior regimen) with a boosted PI with or without one or two NRTIs. DTG must be given twice daily if a patient has certain documented INSTI mutations, or if there is concern about certain mutations (see the Dolutegravir section).
Failed Regimen(s) That Included NRTI(s), NNRTI(s), and PI(s)	**If NRTIs Are Fully Active:** • INSTI plus two NRTIs **If NRTIs Are Not Fully Active:** • INSTI plus two NRTIs with or without an RTV-boosted PI **If There is Minimal NRTI Activity:** • INSTI with or without an RTV-boosted PI with or without ETR or RPV with or without NRTI(s) • Consider adding T-20 and/or MVC if additional active drug(s) are needed.

[a] Exposure to DTG around the time of conception has been associated with a small but significant increase in the risk of infant NTDs. Additional information and specific recommendations about the use of DTG in women and adolescents of childbearing potential and in those who are pregnant or who are trying to conceive are available in the Adult and Adolescent Antiretroviral Guidelines (see Adolescents and Young Adults with HIV and Management of the Treatment-Experienced Patient) and in the Perinatal Guidelines (see Teratogenicity, Recommendations for Use of Antiretroviral Drugs During Pregnancy, and Appendix D. Dolutegravir Counseling Guide for Health Care Providers).

[b] RAL has a low barrier to resistance and requires twice-daily dosing in children and adolescents; BIC and DTG have a higher barrier to resistance and only require once-daily dosing.

Key: 3TC = lamivudine; ART = antiretroviral therapy; ARV = antiretroviral; BIC = bictegravir; DRV = darunavir; DTG = dolutegravir; ETR = etravirine; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NTD = neural tube defect; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; T-20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

Appendix A: Pediatric Antiretroviral Drug Information

Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets

Brand Name by Class	NRTIs						NNRTIs			INSTIs			PIs			PK Enhancers	
	ABC	3TC	ZDV	FTC	TDF	TAF[a]	DOR	EFV	RPV	BIC[a]	DTG	EVG[a]	ATV	DRV	LPV[b]	COBI	RTV
NRTI																	
Cimduo		X			X												
Combivir, Generic		X	X														
Descovy				X		X											
Epzicom, Generic	X	X															
Temixys		X			X												
Trizivir, Generic	X	X	X														
Truvada				X	X												
NRTI/NNRTI																	
Atripla				X	X			X									
Complera				X	X				X								
Delstrigo		X			X		X										
Odefsey				X		X			X								
Symfi or Symfi Lo		X			X			X									
NRTI/INSTI																	
Biktarvy				X		X				X							
Dovato		X									X						
Triumeq	X	X									X						
NNRTI/INSTI																	
Juluca									X		X						
NRTI/INSTI/COBI																	
Genvoya				X		X						X				X	
Stribild				X	X							X				X	
NRTI/PI/COBI																	
Symtuza				X		X								X		X	
PI/COBI																	
Evotaz													X			X	
Prezcobix														X		X	
PI/RTV																	
Kaletra															X		X

Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets

[a] TAF, BIC, and EVG are only available in FDC tablets. However, TAF 25 mg tablets (Vemlidy) are FDA-approved for treatment of HBV. In select circumstances, TAF might be used as one component of a combination ARV regimen, with dosing recommendations similar to those for Descovy.

[b] LPV is only available in FDC tablets or solution.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; BIC = bictegravir; COBI = cobicistat; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FDA = Food and Drug Administration; FDC = fixed-dose combination; FTC = emtricitabine; HBV = hepatitis B virus; LPV = lopinavir; LPV/r = lopinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside and nucleotide reverse transcriptase inhibitor; PI = protease inhibitor; PK = pharmacokinetic; RPV = rilpivirine; RTV = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents (Last updated April 14, 2020; last reviewed April 14, 2020) (page 1 of 4)

This table may include recently approved FDC tablets that have not yet been added to the individual drug sections in Appendix A: Pediatric Antiretroviral Drug Information.

General Considerations When Using FDC Tablets:

- For children weighing ≥25 kg, the Panel recommends using one of the following single-tablet, once-daily regimens: Triumeq (ABC/DTG/3TC), Genvoya (EVG/c/FTC/TAF), or Biktarvy (BIC/FTC/TAF).
- ABC and TAF are favored over ZDV because of the lower risk of NRTI-associated mitochondrial toxicity.
- TDF is more potent than ABC at high viral loads when used in regimens that do not contain an INSTI.
- TAF is favored over TDF because of the lower risk of TDF-associated bone and renal toxicity.
- TDF is generally not recommended for children with SMRs of 1–3 because of TDF-associated bone toxicity; however, for a child weighing <25 kg who can swallow pills, Truvada (FTC/TDF) low-strength tablets offer a reasonable, once-daily alternative to twice-daily ZDV plus 3TC or ABC.
- RPV has low potency at high viral loads, a low barrier to resistance, and requires a high-fat meal for optimal absorption, so EFV or an INSTI are favored over RPV.
- BIC and DTG, the second-generation INSTIs, have a higher barrier to resistance than the first-generation INSTIs EVG and RAL.
- For images of most of the FDC tablets listed in this table, see the Antiretroviral Medications section of the National HIV Curriculum. In addition, a resource from the United Kingdom illustrates the relative sizes of FDC tablets and individual ARV drugs (see the ARV Chart). Although most of the drugs listed in that chart are the same as those in the United States, a few of the brand names are not the same as those listed in Appendix A, Table 2.
- FDC tablets and individual ARV drugs can also be looked up by drug name (brand name and generic) at DailyMed; size is listed under the Ingredients and Appearance section.

INSTI FDC Dosing for Children and Adolescents

Elvitegravir:

- Genvoya (EVG/c/FTC/TAF) is approved by the FDA for children and adolescents weighing ≥25 kg.

Dolutegravir:

- The Panel recommends DTG 50 mg for children and adolescents weighing ≥20 kg (see the Dolutegravir section). The FDA-approved dose is DTG 35 mg for patients weighing ≥30 kg to 40 kg, and DTG 50 mg for patients weighing ≥40 kg.
- For children weighing ≥25 kg, DTG 50 mg can be given as Triumeq (ABC/DTG/3TC) in one large pill or as Descovy (FTC/TAF) plus DTG, which requires two small pills.
- Exposure to DTG around the time of conception has been associated with a small, but significant, increase in the risk of infant NTDs. Additional information and specific recommendations about the initiation and use of DTG in adolescents and women of childbearing potential and in those who are pregnant or who are trying to conceive are available in the Adult and Adolescent Antiretroviral Guidelines (see Table 6b and Adolescents

and Young Adults with HIV) and in the Perinatal Guidelines (see Teratogenicity, Recommendations for Use of Antiretroviral Drugs During Pregnancy, and Appendix D: Dolutegravir Counseling Guide for Health Care Providers).

Bictegravir:

- Biktarvy (BIC/FTC/TAF) is now approved by the FDA for use in children and adolescents weighing ≥25 kg.

FDC by Class Brand name and generic[a] products, when available	**FDC Components**	**Minimum Body Weight (kg) or Age[b]**	**Pill Size (mm x mm) or Largest Dimension (mm)**	**Food Requirements**
NRTI				
Cimduo	3TC 300 mg/TDF 300 mg	35 kg	19	Take with or without food
Combivir and Generic 3TC/ZDV	3TC 150 mg/ZDV 300 mg (scored tablet)	30 kg	18 x 7	Take with or without food
Descovy	FTC 200 mg/TAF 25 mg	**With an INSTI or NNRTI:** • 25 kg **With a Boosted PI:** • 35 kg	12.5 x 6.4	Take with or without food
Epzicom and Generic ABC/3TC	ABC 600 mg/3TC 300 mg	25 kg	21 x 9	Take with or without food
Temixys	3TC 300 mg/TDF 300 mg	35 kg	N/A	Take with or without food
Trizivir and Generic ABC/3TC/ZDV	ABC 300 mg/3TC 150 mg/ZDV 300 mg	40 kg (FDA) 30 kg (Panel)[c]	21 x 10	Take with or without food
Truvada	FTC 200 mg/TDF 300 mg	35 kg	19 x 8.5	Take with or without food
Truvada Low Strength	FTC 167 mg/TDF 250 mg	28 kg	18	Take with or without food
	FTC 133 mg/TDF 200 mg	22 kg	16	Take with or without food
	FTC 100 mg/TDF 150 mg	17 kg	14	Take with or without food
NRTI/NNRTI				
Atripla	EFV 600 mg/FTC 200 mg/TDF 300 mg	40 kg	20	Take on an empty stomach
Complera	FTC 200 mg/RPV 25 mg/TDF 300 mg	35 kg and aged ≥12 years	19	Take on an empty stomach
Delstrigo	DOR 100 mg/3TC 300 mg/TDF 300 mg	Adults	19	Take with or without food
Odefsey	FTC 200 mg/RPV 25 mg/TAF 25 mg	35 kg and aged ≥12 years	15	Take with a meal

Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents (Last updated April 14, 2020; last reviewed April 14, 2020) (page 3 of 4)

FDC by Class Brand name and generic[a] products, when available	**FDC Components**	**Minimum Body Weight (kg) or Age[b]**	**Pill Size (mm x mm) or Largest Dimension (mm)**	**Food Requirements**
NRTI/NNRTI, continued				
Symfi	EFV 600 mg/3TC 300 mg/TDF 300 mg (scored tablet)	40 kg	23	Take on an empty stomach
Symfi Lo	EFV 400 mg/3TC 300 mg/TDF 300 mg	35 kg[d]	21	Take on an empty stomach
NRTI/INSTI				
Biktarvy	BIC 50 mg/FTC 200 mg/TAF 25 mg	25 kg	15 x 8	Take with or without food
Dovato	DTG 50 mg/3TC 300 mg	Adults[e]	19	Take with or without food
Triumeq	ABC 600 mg/DTG 50 mg/3TC 300 mg	40 kg (FDA) 25 kg (Panel)[f]	22 x 11	Take with or without food
NNRTI/INSTI				
Juluca	DTG 50 mg/RPV 25 mg	Adults	14	Take with a meal
NRTI/INSTI/COBI				
Genvoya	EVG 150 mg/COBI 150 mg/FTC 200 mg/TAF 10 mg	25 kg	19 x 8.5	Take with food
Stribild	EVG 150 mg/COBI 150 mg/FTC 200 mg/TDF 300 mg	35 kg and ≥12 years[g]	20	Take with food
NRTI/PI/COBI				
Symtuza	DRV 800 mg/COBI 150 mg/FTC 200 mg/TAF 10 mg	40 kg	22	Take with food
PI/COBI				
Evotaz	ATV 300 mg/COBI 150 mg	35 kg	19	Take with food
Prezcobix	DRV 800 mg/COBI 150 mg	40 kg	23	Take with food
PI/RTV				
Kaletra	**LPV/r Oral Solution:** • LPV 80 mg/mL and RTV 20 mg/mL **Tablets:** • LPV 200 mg/RTV 50 mg • LPV 100 mg/RTV 25 mg	**Post-Menstrual Age of 42 Weeks and a Postnatal Age of ≥14 Days:** • No minimum weight	19	Take with or without food

[a] Size or largest dimension of generic drugs are not listed because they may vary by manufacturer; this information is available by looking up one of the drug components using DailyMed.

[b] Minimum body weight and age are those recommended by the FDA, unless otherwise noted.

[c] Based on the current FDA-approved minimum body weights for the component drugs of Trizivir, the Panel suggests that Trizivir be used at a minimum body weight of ≥30 kg, although it is approved by the FDA for use in children and adolescents weighing ≥40 kg. However, the Panel **does not recommend** using regimens that only contain NRTIs, or using three-NRTI regimens, in children.

[d] Due to PK concerns, the Panel recommends caution when using Symfi Lo in children and adolescents who have SMRs of 1–3 and weigh ≥40 kg (see the Efavirenz section).

Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents (Last updated April 14, 2020; last reviewed April 14, 2020) (page 4 of 4)

[e] The Panel does not currently recommend using Dovato as a 2 drug complete regimen in adolescents and children. This FDC tablet could be used as part of a three-drug regimen in children who meet the minimum body weight requirements for each component drug.

[f] The Panel recommends using DTG 50 mg for children and adolescents weighing ≥20 kg based on available data. However, the doses of ABC and 3TC in Triumeq are too high for children weighing <25 kg (see the Dolutegravir section).

[g] Although Stribild is approved by the FDA for use in children and adolescents weighing ≥35 kg and aged ≥12 years, the Panel **does not recommend** using it in children or adolescents who have SMRs of 1–3.

Key: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; BIC = bictegravir; COBI = cobicistat; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDA = Food and Drug Administration; FDC = fixed-dose combination; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; LPV = lopinavir; LPV/r = lopinavir/ritonavir; N/A = information not available; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NTD = neural tube defect; the Panel = Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV; PI = protease inhibitor; PK = pharmacokinetic; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SMR = sexual maturity rating; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine